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Nanotechnology in the Treatment of Incontinence

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Multiple factors and interrelated mechanisms contribute to natural urinary and fecal continence, a key part of which is played by the urinary and fecal sphincters, respectively. From the engineering point of view, sphincters are simple due to their binary nature: they are either on or off. Thus, engineers see sphincters as analogically even simpler than a water faucet, since no flow regulation is required. From the anatomical point of view, sphincters have multiple interacting parts. The urinary sphincter muscle ensures urinary continence during the filling phase of the bladder. Sphincter abnormalities lead in particular to stress urinary incontinence (SUI), which is defined as involuntary loss of urine during coughing, sneezing, or any other kind of related physical exertion. In severe cases, it presents a continuous loss of urine. Approximately 50% of women older than 20 years have reported urinary incontinence (UI) symptoms, of which 50% of patients are classified as having SUI [1].

Natural fecal continence relies on a complex interplay between the central, peripheral, and autonomous nervous systems, a functioning gastrointestinal (GI) tract, and the anal sphincter complex. The dysfunction of only one of these components can cause the loss of continence control. The overall prevalence of fecal incontinence in adults is reported to be 11–15% and increases with age [2]. Common sources of dysfunction are injuries such as birth trauma, psychological and neurological disorders, and inflammatory diseases of the bowel.

Up to now, nanomedicine in urology and colorectal surgery has primarily been applied in the areas of gene therapy, drug delivery, medical imaging, and thermal ablation of tumors. The application of nanotechnology to the regeneration or replacement of structures in the body is only beginning to progress toward clinical trials. The use of structures with 1–100 nm size features promises to give a specific functionality in the mechanical, electrical, or biochemical regime that is commonly inaccessible on the macroscale. Cellular protein structures and cellular receptor–ligand interactions all exist in the nanoscale regime; nanotechnology can thus be used to provide ligands for cell adhesion. Such integration can lead to an implant

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that is capable of allowing cellular infiltration and the growth of new tissue and blood vessels. A tissue-integrated implant has the advantage of being accessible to defense by the host's immune system. In addition, a biocompatible implant that can be remodeled by macrophages may lead to a reduced inflammatory response directly after implantation.

The application of nanoscale materials to the treatment of incontinence falls into two main functional categories. Within the scope of regenerative medicine, nanotechnology can first be applied to tissue engineering to replace key functions of the organs responsible for continence. This ranges from the development of an improved material for a pubovaginal sling that eventually integrates into host tissue, to a complete sphincter reconstruction. Second, nanotechnology can be applied to the development of artificial sphincter implants for cases of severe incontinence. Based on their versatility, reaction speed, reaction forces, as well as energy consumption, smart materials such as low-voltage electroactive polymers can be used to produce artificial muscles for sphincter replacement.

In this chapter, we examine the treatment of urinary and fecal incontinence, from the perspective of nanotechnology-based interventions. Both sections are arranged according to the same structure. We first introduce the incontinence etiology and assessment, as well as the underlying physics of incontinence. This forms the basis for the subsequent discussion on the application of nanotechnology to incontinence treatment by tissue engineering or alternatively through the engineering of a sphincter replacement device.

15.1 Urinary Incontinence

15.1.1 Urinary Incontinence Etiology

An intact urinary continence consists of a complex interplay of the central, peripheral, and autonomous nervous systems. The dysfunction of only one of these components can cause UI. Congenital or acquired anatomical malformations can also cause UI. In general, five types of UI can be differentiated. Most frequent are SUI and urge incontinence, which together account for 90% of instances. The other 10% of instances are the result of the three less frequent causes: neurogenic incontinence, overflow incontinence, and anatomical malfunctions. A clinician has to distinguish between two main categories of urinary incontinence: temporary or persistent UI (see Table 15.1). The general risk factors are listed in Table 15.2 [3].

15.1.2 Urinary in-/Continence Assessment

It is important to determine, which of the five types of UI, that is, stress, urge, overflow, neurogenic, or anatomical UI, the patient has, as this identification will

Table 15.1 Possible causes of UI are classified into two main groups: temporary and persistent.

Temporary UI	Diuretic drinks, food or medications: Caffeine Decaffeinated and/or carbonated drinks Alcohol Artificial sweeteners Blood pressure medications, sedatives Large doses of vitamins B or C Fruits high in spice, acid, or sugar Urinary tract infection: Due to irritation of the bladder a strong urge to urinate can be caused.
	Constipation: Rectum and bladder share some nerves that can be irritated by stool impaction. This can cause an increase in urination.
Persistent UI	Pregnancy: Increased weight of uterus and changes in hormones may increase UI. Childbirth: Muscles needed for bladder control may be weakened by vaginal delivery. Age: With age muscles need for bladder control may be weakened. Menopause: Loss of estrogen can cause a deterioration of the urogenital tract and thereby an increase of UI. Hysterectomy: Removal of the uterus can damage supporting pelvic floor muscles. Enlarged prostate: Especially in older men benign prostate hyperplasia can cause UI. Prostate cancer: UI can be caused by prostate cancer itself because of infiltration and because of medication or radiation. Obstruction: Any obstruction can lead to overflow incontinence. Neurological disorders: Parkinson's disease, stroke, brain tumours, multiple sclerosis and spinal injuries can interfere with pelvic floor innervation.

guide treatment decisions. The most essential step to UI identification is a detailed anamnesis, in which questions regarding frequency of urination and the ability to hold back urine play an important role. Quite frequently, physicians recommend that patients fill out *bladder diaries* to record the amount of drinks

Table 15.2 General risk factors for UI are gender, age, body weight, and diseases.

Gender	Women > men (pregnancy, childbirth, changes in hormones, and normal female anatomy)
Age	With age muscles shrink. So with age muscles of bladder and urethra lose their strength.
Body weight	With overweight pressure on the bladder increases and urine may get released.
Diseases	Neurological disorders including stroke or metabolic diseases such as diabetes may increase risk of UI by reducing nerve functions.

and urine, the frequency of urination, or whether the patient felt urge to urinate. The patient is also requested to record episodes of incontinence.

The determination of the patient's history is followed by physical examinations. Conditions such as prolapses and loss of urine, while coughing, can be easily assessed. Further exams include a urinalysis to check on signs of infection and other abnormalities and a postvoid urination residual measurement using a catheter or ultrasound to evaluate the amount of leftover urine in the patient's bladder. A large amount of leftover urine may be a sign of an obstruction in the urinary tract. Nerve or muscular problems can also cause urinary leftover.

Further specialized tests may be recommended including urodynamic testing and cystoscopy. With an urodynamic test, the strength and urinary sphincter health can be assessed and the type of UI can be distinguished. After application of a catheter, the patient's bladder is filled with water, while the pressure within the bladder is measured. In a cystoscopy test, a thin scope is inserted into the urethra and bladder to check the structure of these organs and, if necessary, to remove abnormalities. A cystogram reveals structural and functional problems of the urinary tract through injecting a radiopaque material in the urethra and bladder.

Finally, a pelvic ultrasound can be used to check for abnormalities of the patient's genitals and urinary tract, and magnetic resonance imaging (MRI) can give evidence of dyssynergies and further pathologies of the pelvic floor such as entero-, recto-, or cystoceles. An MRI examination is extensive and relatively expensive, therefore, it is usually only used in cases, where more complex pathologies are suspected [4–6].

15.1.3 Physics of Urinary Continence

The urinary sphincter is composed of a thin inner layer and a thick outer layer. The inner layer consists of smooth muscle cells, whereas the outer layer consists of striated muscle (RS) cells, which supports slow contractions around the urethra. The mechanical properties of urethral tissue are characterized by the tissue's stress–strain relation. The stress–strain relation can be measured by a conventional tensile testing machine, by compression, and *in vivo* by aspiration. In the simplest case, from the stress–strain curve measured by these methods, the Young's modulus can be determined by inverse finite element modeling.

The human urethra consists of anisotropic, viscoelastic tissue exhibiting an inner diameter of about 5 mm and an outer one of about 12 mm. As a rough approximation, one can assume that the leakage starts, when the external sphincter pressure equals the intravesical pressure. The tissue of the urethra, however, can act against or with the external pressure. This means that a higher or lower external pressure is necessary to close the urethra. This difference arises from the wall pressure p_W along the sphincter length L and from the stress of the urethra at both ends characterized by the rim force F_R. Since the inner part of the urethra can be closed on the length, which is smaller or larger than the

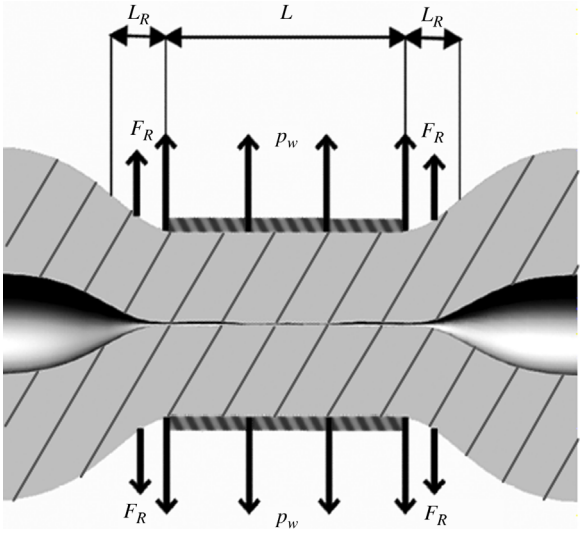

Figure 15.1 Physical parameters of the urethral compression. (Model from Ref. [7].)

sphincter length L, one has introduced the rim length L_R equally present on both sides of the sphincter. This empirical model, known as the *urethra compression model*, contains three parameters, which can be positive and negative, to be determined on the basis of well-defined experiments (see Figure 15.1) [7].

15.1.4
Tissue Engineering and Sling Material for Sphincter Regeneration

The most common surgical treatment for SUI is the placement of a suburethral pubovaginal sling. Sling placement helps to stabilize the urethrovescial junction and compresses the urethral lumen during stress manuveurs. Sling materials include autografts, allografts, that is, cadaveric tissues, xenografts including porcine small intestinal submucosa, and synthetic materials. However, the ideal sling material has still not been identified. Such a material would be strong, readily available, with low occurrences of infection, immunologic rejection, and erosion. Potential advantages of a tissue engineered sling material include reduced donor site morbidity and customizable biomechanical properties.

A key application of tissue engineering (TE) is to replace diseased tissue with a highly porous three-dimensional scaffold that mimics some functions of the extracellular matrix (ECM) so as to promote cell growth and host tissue infiltration. Synthetic polymeric scaffolds such as electrospun polyethylene terephthalate and polyurethane, for example, have a fibrous microarchitecture similar to the ECM. Two potential scaffolds that have been proposed as optimal sling materials for SUI treatment are poly(L)lactic acid (PLA) and small intestinal submucosa (SIS) [8–10]. Both were found to support cell attachment and

proliferation, and had biomechanical properties similar to that of the pelvic floor. Unlike SIS, often derived from porcine sources, PLA is a synthetic material.

Engineering a synthetic sling material with nanometer scale features requires suitable microfabrication techniques, such as electrospinning and 3D printing. Electrospinning is one variation of electrospray techniques and is commonly used to produce nano- and micrometer-size fibers suitable for the fabrication of a scaffold. A syringe is loaded with polymer solution, and a high voltage source is used to extract a stream of polymer from the needle tip toward a collector plate. The plate can be moved to create various fiber orientations, allowing the formation of three-dimensional scaffolds. Electrospinning in combination with heat annealing has been used to produce a PLA scaffold with mechanical properties comparable to native tissue [8].

As less invasive alternatives to sling placement, research directions analogous to those for the application of TE to fecal sphincter regeneration have also been pursued. These directions aim toward directly improving urinary sphincter defects by injection of bulking agents, or by the injection of stem cells, progenitor cells, or adult cells [11]. For both approaches, nanotechnology has the potential to advance progress through structures that are bioengineered down to the nanometer scale.

Bulking agents with nanofeatures have demonstrated advantages [12,13]. Kim *et al.* used growth factor-immobilized porous beads with sizes of 200–300 μm and pores of 25–50 μm as a bioactive bulking agent to treat SUI. They were found to be effective for the regeneration of smooth muscle around the urethra, and lead to functional recovery through an improved contractile response [12]. This is likely due to the combination of (i) the bead's high porosity and the interconnectivity provides an appropriate environment for cell adhesion and proliferation, and (ii) the sustained release of growth factors promotes differentiation into target cells. Similarly, Park *et al.* showed that a hybrid hydrogel consisting of *in situ* forming gelation-based macrogels and self-assembled heparin-based nanogels as a carrier allowed for sustained release of growth factors as well as a bulking effect [13]. In a similar manner, the effective introduction of stem cells relies on seeding onto the appropriate structural support, the fabrication of which can be aided by nanotechnology. Designing features in the natural length scale of proteins can make available better cell-substrate interaction, thus leading to improved biocompatibility. In a recent study, adipose derived stem cells (ADSC) were harvested and seeded onto poly (lactic-coglycolic acid) (PLGA) microparticles containing nerve growth factor (NGF). The preparation was injected periurethrally into mice, and improved the leak-point pressure (LPP) to (22.5 ± 6.1) cm H_2O over treatments without either PLGA or NGF [14]. PLGA is a copolymer of PLA and poly glycolic acid (PGA), and is a well-introduced biomaterial often used for drug delivery. With continuing advancement in nanofabrication techniques, promising scaffold materials such as PLGA and PLA can be engineered with increasingly advanced nanoscale features conducive to cell growth and proliferation as well as oxygen exchange and nutrient delivery.

15.2
Fecal Incontinence

15.2.1
Fecal Incontinence Etiology

An intact continence consists of a complex interplay of central, peripheral, and autonomous nervous system, a functioning GI tract and anal sphincter complex. A dysfunction of only one of these components can cause a fecal incontinence (FI). A clinician has to distinguish between congenital and acquired risk factors of FI. Congenital risk factors include Hirschsprung's disease or anorectal malformations, whereas acquired risk factors may be conditions after sphincter lesions during delivery, radiation, or previous surgeries (cf. Table 15.3) [15].

15.2.2
Physics of Fecal Continence

The mechanisms and factors contributing to normal continence are multiple and inter-related. Loss of control of continence is called fecal incontinence that for instance may be caused by injuries like birth trauma or previous surgeries, psychological or neurological disorders or inflammatory diseases of the bowel [15]. The curved anatomy of the rectum and the three layers of closure mechanism enable continence. A schematic illustration of the main continence structures is shown in Figure 15.2. The curved anatomy of the rectum is caused by the puborectal sling, which pulls the rectum towards the *os pubis*. The closing mechanism includes an outer, middle, and inner layer. The outer layer narrows the anal canal, and consists of the puborectal sling, *m. levator ani*, and the circular external anal sphincter muscle (EAS). The EAS is a voluntary muscle that can double the pressure in the anal canal during contraction for a short period of time. The pudendal nerve originating from the sacral cord S4 innervates the EAS.

Table 15.3 Risk factors for FI can be classified as either congenital or acquired.

Congenital risk factors	Hirschsprung's disease
	Spina bifida
	Anorectal malformations
Acquired risk factors	Surgeries of the lesser pelvis (rectum resection; hysterectomy)
	Radiation
	Injuries of the sphincter organ (iatrogenic, i.e., hemorrhoidectomy, surgery of fistula, sphincterotomy; trauma during delivery)
	Gastrointestinal diseases (inflammatory bowel diseases; irritable colon)
	Neurological incontinence (diabetes mellitus; cerebral insult; spinal trauma; Parkinson's disease; multiple sclerosis)
	Age

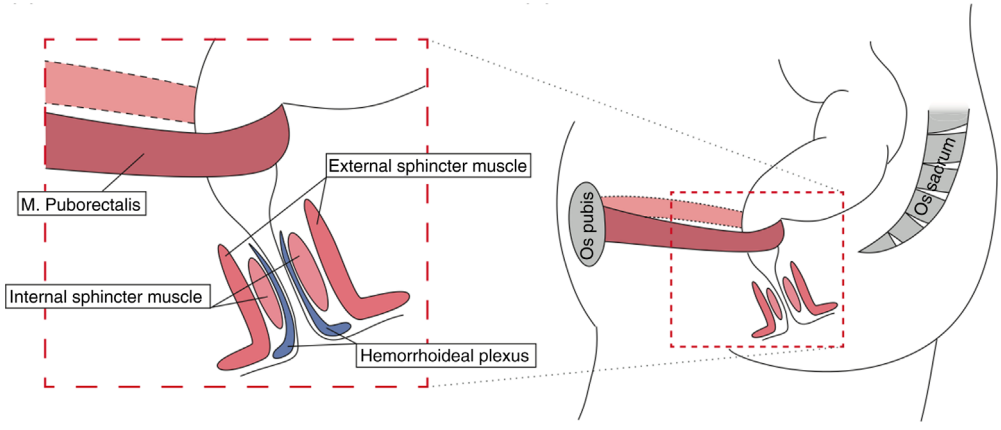

Figure 15.2 Schematic representation of the anatomical structures involved in continence (adapted from Ref. [16]). The three layers forming the closure mechanism are shown in detail in the expanded view. The muscular structures are rose-colored, while the hemorrhoideal plexus is shown in blue.

The middle layer consists of *m. sphincter ani internus* (IAS), an involuntary muscle contributing about 55% of the resting anal pressure. Together with the inner layer consisting of the hemorrhoidal vascular cushion, the IAS maintains continence, notably for gases and liquids. The parasympathetic fibers originating from the sacral cord and the sympathetic fibers originating from the lumbar cord innervate the IAS [17]. The hemorrhoidal vascular cushion consists of arterial–venous vessels that are filled by contraction of the venous vessels. When filled, the hemorrhoidal cushion forms the so-called *corpus cavernosum recti*, and closes the anal canal completely.

The rectoanal inhibitory reflex (RAIR) is an involuntary IAS relaxation in response to the filling of the rectum. Receptors stimulated by distension initiate the reflex, allowing stool to descend into the anal canal, where other specialized receptors respond to stool consistency. To avoid complete evacuation a semi-voluntary rectoanal excitatory reflex (RAER) of the EAS and *m. puborectalis* follows the RAIR. Other mechanisms of continence include the antiperistaltic function of the sigmoid, which causes the rectum to stay empty, and specialized receptors in the rectum and anal canal that detect, where stool is present and its consistency. Finally, rectoanal reflexes and the defecation cycle enable a complete evacuation of stool from the rectum and anal canal [17].

15.2.3
Fecal in-/Continence Assessment

An essential part of diagnosis is a detailed anamnesis. Questions regarding frequency of defecation and the ability to hold back flatus and stool form part of the anamnesis. Inspection is the easiest and often also most important part of

the diagnostic procedure, allowing direct signs of incontinence such as erythema, scars, or smearing to be detected immediately. Also a part of every examination is rectal palpation, as it allows divergent pressures due to lesions of the sphincter or irregularities in the structure of the anal canal to be found.

Sphincter function can be measured and quantified by manometry. A decreased resting pressure, as well as an insignificant increase of squeezing pressure, can be a sign of a dysfunctional sphincter. An extremely elevated resting pressure can embody a pelvic floor dyssynergy. Besides the simple anal manometry, gastroenterologists also use 3D manometry with fillable balloons. In this way, rectal capacity and/or rectal sensibility can be assessed. This information can be used to draw conclusions on the existence of a rectal reservoir or if the patient is already overreacting to minimal volumes. Endoanal ultrasound (EUS) allows the volume and the integrity of the entire sphincter system to be examined. Defects such as scars including their dimension, as well as the different compounds and layers of the sphincter system, can all be detected with relative ease. In addition, contrast agents can be brought into fistulas to determine the extent of disease. MRI, in particular MR-defecography, is a continuous examination technique, delivering dynamic images during evacuation. Examination by MRI can provide evidence of dyssynergies and further pathologies of the pelvic floor. The rectum is first filled with a paste-like contrast agent; evacuation of this contrast agent allows pelvic floor pathologies such as entero-, recto-, or cystoceles to be clearly identified. However, the MRI examination is extensive, relatively expensive, and embarrassing for patients. Therefore, it is only applied for cases, where other clinical examinations and anamnesis substantiate suspicion of more complex pelvic floor pathologies.

15.2.4 Tissue Engineering for Sphincter Regeneration

As in the case for the treatment of urinary incontinence, key tissue engineering methods from regenerative medicine have also been applied to the treatment of fecal incontinence. These efforts range from regenerating the fecal sphincter through minimally invasive means using injectable scaffolds [18] to bioengineering transplantable rings of IAS tissue [19,20]. Therapeutic approaches entirely based on injecting cells into the anal sphincter have given mixed results. One of the first was carried out by Frudinger *et al.*, who performed a clinical study with a 12-month follow-up on 10 women with FI [21]. They found that after autologous myoblasts were injected into the EAS, there was an initial increase in anal squeeze pressure, and there was no sustained physiological change observed after one year. The lack of long-term regeneration suggests the failure of the cells to integrate into host tissue.

To increase the likelihood of engrafting viable cells to the injured sphincter, cells can be combined with a biocompatible scaffold. Studies have shown that the three-dimensional structure of a scaffold is of critical importance to cell adhesion, proliferation, and differentiation [22]. Nanotechnology can be applied

to engineer structural elements of the injectable scaffold, including the pore size, porosity, and surface topography. Ahmadi *et al.*, for example, fabricated macroporous PLGA microspheres as a cell carrier for the transplantation of smooth muscle cells to improve sphincter contractility [23]. They reported enhanced attachment, growth, and migration of smooth muscle cells compared to microcarriers of porcine gelatin, due in part to the specific nature of the cell–scaffold interaction on the PLGA microsphere surface.

Nonetheless, further studies are required to find an optimized bioengineered cell–scaffold therapy, as evidenced by the recent study of Kang *et al.*, one of the first studies to examine whether bioengineering can improve fecal incontinence [24]. In this work, porous polycaprolactone beads containing autologous myoblasts were injected into a dog model of FI. Although they used well-characterized microcarriers, Kang *et al.* did not find any significant improvement in sphincter function, as the injected myoblasts failed to integrate into the host sphincter.

Finally, attempts have been made to bioengineer transplantable tissue. Fibrin gels are formed by the self-assembly of fibrin monomers into fibrils, which, under appropriate conditions, organize themselves into a matrix suitable for contractile tissue growth. Cells migrate into the matrix and proliferate, eventually replacing the fibrin with their own extracellular matrix. Hecker *et al.* found that IAS rings bioengineered from smooth muscle cells grown on a fibrin matrix generated a spontaneous basal tone, and demonstrated physiological functionality similar to IAS smooth muscle *in vivo* [19]. Potential limitations include finding suitable sources of smooth muscle cells, and the time required to produce the IAS structures.

As in the case of TE for the treatment of urinary incontinence, nanotechnology has the potential to advance both approaches described in this section through structures that are bioengineered on the nanometer scale. First, by fabricating biocompatible synthetic carriers that promote the transplantation of cells to host tissue, as well as tissue bulking, and second, by providing scaffolds with microenvironments designed to enhance cell proliferation and integration, as well as neovascularization. However, TE solutions for FI, including those involving nanotechnology, are currently less advanced than similar solutions for urinary incontinence.

15.2.5
Dielectric Elastomer Actuators for Sphincter Replacement

Nanotechnology as an advanced tool for the creation of nanoscale-engineered structures is appropriate not only to scaffolds for the regeneration of functional tissue, but also as artificial replacements of the functional tissue itself. In the treatment of incontinence, nanotechnology can be used to fabricate adaptive sphincters. Dielectric elastomer actuators (DEA) are one candidate for these so-called smart implants. Advantages offered by DEAs as artificial sphincter compared to currently available sphincters are superior actuator properties such as millisecond response time, mechanical strain of more than 10%, and the

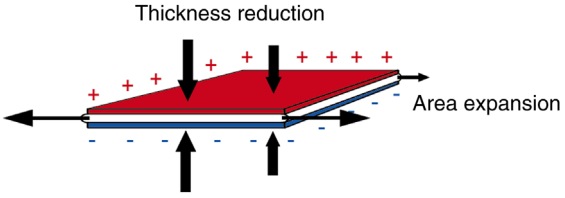

Figure 15.3 Operating principle of a DEA. A voltage applied across the electrodes results in their attraction by the electrostatic force. The electrodes squeeze the incompressible elastomer between them, resulting in a lateral area expansion.

power-to-mass densities similar to natural muscles. Thus, DEAs are popularly referred to as *artificial muscles*, and offer promising perspectives for biomimetic applications because of the large actuations and sensing ability.

Physically, DEA are capacitors that change their capacitance when a voltage is applied, due to a shape change of the polymer sheet in the electric field, namely, its thickness decreases and its area expands. A stretchable dielectric film is sandwiched between compliant electrodes, forming a planar structure. Applying a voltage across the electrodes induces a mutual electrostatic attraction between them that squeezes the elastomer laterally, as illustrated in Figure 15.3. This lateral expansion is large; depending on the elastomer, a 100% increase in area is possible.

Dielectric elastomer actuators operating at voltages as low as tens of volts will enable their widespread application as medical implants. To reduce the currently used operating voltage by two orders of magnitude or even more, research efforts have primarily been directed toward modifying the elastomers' dielectric permittivity. An alternative, physically motivated approach is to reduce the thickness of the elastomer layer itself. Such an approach is faced with two major technical challenges, both of which can be approached using the tools of nanotechnology. The first technical challenge is in making homogenous elastomer films with thicknesses in the regime of several hundred nanometers or below. This reduction of thickness will allow the actuation voltage to be reduced from the kV regime to medically acceptable values below 42 V. This can be seen by considering the relation between the electromechanical pressure p_m, the applied voltage U, and the elastomer film thickness h_{ef}:

$$p_m = \varepsilon \cdot \varepsilon_0 \cdot E^2 = \varepsilon \cdot \varepsilon_0 \cdot \frac{U^2}{h_{ef}^2},$$

where ε is the relative permittivity of the dielectric elastomer, ε_0 is the free space dielectric permittivity, and E is the induced electric field [25]. By reducing h_{ef} from the micrometer regime to the nanometer regime, the voltage can be similarly reduced from the kV-regime to the order of several volts, while maintaining a comparable strain, which is proportional to p_m:

$$s_{x,y} = -0.5\, s_z = \frac{\Delta h_{ef}}{2h_{ef}} = \frac{p_m}{2Y},$$

where $s_{x,y}$ is the strain in the planar directions, s_z is the strain in the thickness direction, and Y is the elastic modulus of the polymer. This relationship is valid for an incompressible polymer and small strains s_z [25].

To give a comparable force to the micrometer-thin actuators, thousands of nanometer-thin layers operating in parallel are required. Such large-scale stacking demands a homogeneity and reproducibility that can be achieved by a well-controlled fabrication process. As known from micro- and optoelectronics, molecular beam deposition (MBD) is such a process. MBD is often the key development step before the establishment of a mass industrial technique such as chemical vapor deposition (CVD). Töpper *et al.* recently presented the use of MBD to fabricate single-layer polydimethylsiloxane (PDMS) nanometer-thick films, showing that these films respond at less than 20 V [26]. The next step to this preliminary result is the growth of reliable actuators by MBD.

Alternative methods are also being investigated. Weiss *et al.* demonstrated that alternating current, electrospray deposition allows for the fabrication of homogenous, flat, nanometer-thin PDMS films [27]. The growth of the PDMS with the average molecular weight of 6000 g/mol at deposition rates ranging from 0.02 to 5.54 nm/s was *in situ* monitored by means of spectroscopic ellipsometry.

The second technical challenge is in making flexible electrodes. Due to the requirement for conductivity, metals are traditionally used as the electrode material. However, even if a metal electrode is 10 times thinner than the elastomer, the mechanical properties of the actuator will still be dominated by the stiffness of its metal electrodes. This is illustrated in Figure 15.4, where the effective

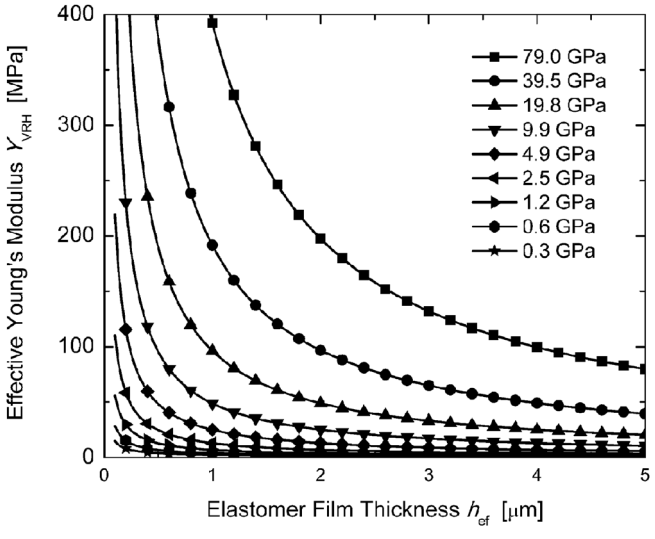

Figure 15.4 Plot of the Voigt-Reuss-Hill effective Young's modulus as a function of the elastomer film thickness h_{ef}, for a 10 nm thick electrode. The elastomer has a constant Young's modulus of 1 MPa. The effect of varying the Young's modulus of the electrode from 0.3 to 79.0 GPa is indicated by the different symbols. (Adapted from Ref. [28].)

Young's modulus (Voigt–Reuss–Hill average) Y_{VRH} of an elastomer with 10 nm of electrode has been calculated as a function of the thickness of the elastomer. In these plots, the Young's modulus of the elastomer is held constant at 1 MPa, while that of the electrode is varied from 0.3 to 79.0 GPa, which is the Young's modulus of gold (square symbols).

Thus, there is a need to find alternative electrodes that are more flexible than isotropic metal electrodes. Electrodes with nanostructured wrinkles have been demonstrated to exhibit a larger actuation and improved stress–strain behavior compared to planar electrodes [28]. Nonconventional electrode materials such as liquid metals or graphene belong to the alternative solutions.

References

1 Dooley, Y., Kenton, K., Cao, G., Luke, A., Durazo-Arvizu, R., Kramer, H., and Brubaker, L. (2008) Urinary incontinence prevalence: results from the National Health and Nutrition Examination Survey. *J. Urol.*, **179**, 656–661.

2 Macmillan, A.K., Merrie, A.E., Marshall, R.J., and Parry, B.R. (2004) The prevalence of fecal incontinence in community-dwelling adults: a systematic review of the literature. *Dis. Colon Rectum*, **47**, 1341–1349.

3 DuBeau, C.E. (2014) Epidemiology, risk factors, and pathogenesis of urinary incontinence. www.uptodate.com/home (accessed March 5).

4 AskMayoExpert (2013) *What Tests Are Needed to Confirm the Diagnosis or Expedite the Evaluation of Female Incontinence?* Mayo Foundation for Medical Education and Research, Rochester, MN.

5 AskMayoExpert (2013) *What Tests Are Needed to Confirm the Diagnosis or Expedite the Evaluation of Male Incontinence?* Mayo Foundation for Medical Education and Research, Rochester, MN.

6 Hersh, L. and Salzman, B. (2013) Clinical management of urinary incontinence in women. *Am. Fam. Physician*, **87**, 634–640.

7 Marti, F., Leippold, T., John, H., Blunschi, N., and Müller, B. (2006) Optimization of the artificial urinary sphincter: modeling and experimental validation. *Phys. Med. Biol.*, **51**, 1361–1375.

8 Mangera, A., Bullock, A.J., Roman, S., Chapple, C.R., and MacNeil, S. (2013) Comparison of candidate scaffolds for tissue engineering for stress urinary incontinence and pelvic organ prolapse repair. *BJU Int.*, **112**, 674–685.

9 Roman, S., Mangera, A., Osman, N.I., Bullock, A.J., Chapple, C.R., and MacNeil, S. (2014) Developing a tissue engineered repair material for treatment of stress urinary incontinence and pelvic organ prolapse – which cell source? *Neurourol. Urodyn.*, **33**, 531–537.

10 Jankowski, R., Pruchnic, R., Hiles, M., and Chancellor, M.B. (2004) Advances toward tissue engineering for the treatment of stress urinary incontinence. *Rev. Urol.*, **6** (2), 51–57.

11 Lin, C.-S. and Lue, T.F. (2012) Stem cell therapy for stress urinary incontinence: a critical review. *Stem Cell Dev.*, **21** (6), 834–843.

12 Kim, I.G., Oh, S.H., Lee, J.Y., Lee, J.Y., and Lee, J.H. (2011) Bioactive porous beads as an injectable urethral bulking agent: in vivo animal study for the treatment of urinary Incontinence. *Tissue Eng. Part A*, **17** (11–12), 1527–1535.

13 Park, K.M., Son, J.Y., Choi, J.H., Kim, I.G., Lee, Y., Lee, J.Y., and Park, K.D. (2014) Macro/nano-gel composite as an injectable and bioactive bulking material for the treatment of urinary incontinence. *Biomacromolecules*, **15**, 1979–1984.

14 Thaker, H. and Sharma, A.K. (2013) Regenerative medicine based applications

to combat stress urinary incontinence. *World J. Stem Cells*, **5** (4), 112–123.
15 Gingert, C. and Hetzer, F.H. (2014) Stuhlinkontinenz. *Coloproctology*, **36** (2), 125–137.
16 Fattorini, E., Brusa, T., Gingert, C., Hieber, S.E., Leung, V., Osmani, B., Dominietto, M.D., Büchler, P., Hetzer, F., and Müller, B. (2016) Artificial muscle devices: innovations and prospects for fecal incontinence treatment. *Ann. Biomed. Eng.*, **44**, 1355–1369.
17 Fleshman, J.W. and Wolff, B.G. (2007) *The ASCRS Textbook of Colon and Rectal Surgery*, Springer.
18 Bitar, K.N. and Zakhem, E. (2014) Design strategies of biodegradable scaffolds for tissue regeneration. *Biomed. Eng. Comput. Biol.*, **6**, 13–20.
19 Hecker, L., Baar, K., Dennis, R.G., and Bitar, K.N. (2005) Development of a three-dimensional physiological model of the internal anal sphincter bioengineered *in vitro* from isolated smooth muscle cells. *Am. J. Physiol. Gastrointest. Liver Physiol.*, **289**, G188–G196.
20 Raghavan, S., Miyasaka, E.A., Gilmont, R.R., Somara, S., Teitelbaum, D.H., and Bitar, K.N. (2014) Perianal implantation of bioengineered human internal anal sphincter constructs intrinsically innervated with human neural progenitor cells. *Surgery*, **155**, 668–674.
21 Frudinger, A., Kolle, D., Schwaiger, W., Pferfer, J., Paede, J., and Halligan, S. (2010) Muscle-derived cell injection to treat anal incontinence due to obstetric trauma: pilot study with 1 year follow-up. *Gut*, **59**, 55–61.
22 Parmar, N., Kumar, L., Emmanuel, A., and Day, R.M. (2014) Prospective regenerative medicine therapies for obstetric trauma-induced fecal incontinence. *Regen. Med.*, **9**, 831–840.
23 Ahmadi, R., Mordan, N., Forbes, A., and Day, R.M. (2011) Enhanced attachment, growth and migration of smooth muscle cells on microcarriers produced using thermally induced phase separation. *Acta Biomater.*, **7**, 1542–1549.
24 Kang, S.-B., Lee, H.S., Lim, J.-Y., Oh, S.H., Kim, S.J., Hong, S.-M., Jang, J.-H., Cho, J.-E., Lee, S.-M., and Lee, J.H. (2013) Injection of porous polycaprolactone beads containing autologous myoblasts in a dog model of fecal incontinence. *J. Korean Surg. Soc.*, **84**, 216–224.
25 Pelrine, R., Kornbluh, R., and Joseph, J. (1998) Electrostriction of polymer dielectrics with compliant electrodes as a means of actuation. *Sens. Actuators A*, **64**, 77–85.
26 Töpper, T., Weiss, F.M., Osmani, B., Bippes, C., Leung, V., and Müller, B. (2015) Siloxane-based thin films for biomimetic low-voltage dielectric actuators. *Sens. Actuators A*, **233**, 32–41.
27 Weiss, F.M., Töpper, T., Osmani, B., Peters, S., Kovacs, G., and Müller, B. (2016) Electrospraying nanometer-thin elastomer films for low-voltage dielectric actuators. *Adv. Electron. Mater.*, 1500476. doi: 10.1002/aelm.201500476.
28 Osmani, B., Töpper, T., Deschenaux, C., Nohava, J., Weiss, F.M., Leung, V., and Müller, B. (2015) Micro- and nanostructured electro-active polymer actuators as smart muscles for incontinence treatments. *AIP Conf. Proc.*, **1646**, 91–100.