Effective spring constants for the elastically coupled insertions in membranes.

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1 Introduction

Membrane-spanning peptides such as the ion channel gramicidin dimer, cause membrane deformation which contribute significantly to both the energetics of the insertion and the membrane-mediated interaction between the channels. Recently, interest in this field shifted from study of individual channels to study of collective effects in channel kinetics. Here we discuss an efficient way to describe the membrane-mediated interaction between the insertions in terms of coupled harmonic oscillators and corresponding "spring constants".

2 Variational principle, boundary conditions and Euler-Lagrange equation.

We consider an elastic system extended in $x, y$–plane, where the deformation can be described by a 2–dimensional field of "vertical" displacement $u(r)$ ($r = (x, y)$ is the radius vector in the mid-plane of the system). The examples include smectic and similar models for lipid bilayers, and "floating plate" model of classical elastic theory (see [1] for review).

The elastic boundary problem can be formulated as a variational (minimum) principle for the energy functional

$$F^{(2)}[u] = \int g^{(2)}(u, \nabla u, \Delta u, ...) df$$

where $g^{(2)}$, the surface density of the elastic energy, is a quadratic function of the surface displacement $u$ and its derivatives. We will consider a membrane with $N$ cylindrical insertions, assuming that on the contour $\gamma_i$ of $i$–th insertion both $u(r)$ and $\nabla u(r)$ are fixed functions of $r_{\gamma_i}$, the position vector for the points belonging to $\gamma_i$. It leads to the boundary conditions

$$u(r)|_{r_{\gamma_i}} = u_i(r_{\gamma_i})$$

$$\nabla u(r)|_{r_{\gamma_i}}^n = s_i(r_{\gamma_i})$$
"n" designates the direction normal to $\gamma_i$ at the point $\mathbf{r}_i$. Note that the vertical displacement $u_i$ in the immediate contact of a membrane with an inserted peptide is typically described by the "hydrophobic matching condition" leading to a particular case of Eq. 2 with $u_i(\mathbf{r}_i) = u_0 = \text{const.}$

Additional conditions on the external membrane boundary (designated as $\gamma_\infty$) are:

$$u(\mathbf{r})|_{\gamma_\infty} = 0 \quad (4)$$

$$\nabla u(\mathbf{r})|_{\gamma_\infty} = 0 \quad (5)$$

In many cases, including the biharmonic problem with smooth and continuous boundaries that we consider ([4], Ch. 6), the variational principle $\delta F = 0$ (the minimum condition for the energy functional) leads to the Euler-Lagrange equation which we present for now as

$$L(u) = 0 \quad (6)$$

where $L$ is a linear differential operator. The elastic energy $E = \min F = \min F[u]$ is the value of $F[u]$ calculated with the solutions of Eqs. 2-3 in place of $u$. We will show now that in some important cases $E$ can be explicitly presented as a quadratic form of the boundary parameters, such as $u_i$ and $s_i$.

3 Effective spring constants

3.1 Boundary displacements and contact slopes fixed to constants

Suppose now that the boundary displacements and the contact slopes are fixed at the $i-th$ insertion to the constants $u_i$ and $s_i$. Some preliminary results for this case were reported in [5]. Eqs. 2-3 can be written as

$$u(\mathbf{r})|_{\gamma_i} = u_i \quad (7)$$

$$\nabla u(\mathbf{r})|_{n_{\gamma_i}} = s_i \quad (8)$$

We now introduce the "superfinite" elements, $\phi_i^u(\mathbf{r})$ and $\phi_i^s(\mathbf{r})$, solutions of Eq. 4 satisfying boundary conditions Eq. 4-5 and following conditions at the internal boundaries:

$$\phi_i^u(\mathbf{r})|_{\gamma_k} = \delta_{ik}, \quad \nabla \phi_i^u(\mathbf{r})|_{n_{\gamma_k}} = 0 \quad (9)$$

1Which means that $L \cdot (c_1 u_1 + c_2 u_2) = c_1 L \cdot u_1 + c_2 L \cdot u_2$ ($c_1$ and $c_2$ are the arbitrary constants). The linearity does not impose, however, any restrictions on the order of the differential equation (which for most of the applications considered is bi quadratic).
\[ \phi_i^s(r)\big|_{\gamma_k} = 0, \quad \nabla \phi_i^s(r)\big|_{\gamma_k} = \delta_{ik} \quad (10) \]

where \( \delta_{ik} \) is the Kronecker symbol. The solution of Eqs. 6-5, 7, 8 can be written as a linear combination of the superfinite elements:

\[ u(r) = \sum_{i=1}^{N} (u_i \phi_i^u(r) + s_i \phi_i^s(r)) \quad (11) \]

Substituting this result into Eq. 1 allows presenting \( E \) as a quadratic form of the boundary parameters:

\[ E = \sum_{i=1}^{N} \sum_{j=i}^{N} c_{ij}^{\alpha\beta} \alpha_i \beta_j \quad (12) \]

where \( c_{ij}^{\alpha\beta} \) are the effective spring constants describing interaction between the insertions \( i \) and \( j \) (\( c_{ii}^{\alpha\beta} \) corresponds to the "self energy" of the \( i \)-th insertions). Such a "linear spring model" was first introduced for a single insertion in [3] and later generalized in [5]. Eq. 12 implies that the additional summation is performed over the repeated indexes, \( \alpha, \beta \) (= \( u, s \)).

The effective spring constants satisfy the symmetry relation

\[ c_{ij}^{\alpha\beta} = c_{ji}^{\beta\alpha} \text{ and, consequently, } c_{ij}^{\alpha\beta} = c_{ji}^{\alpha\beta}. \quad (13) \]

As an illustration, consider the expression for \( g^{(2)} \) which is typical in study of membranes:

\[ g^{(2)} = B (\Delta u)^2 + A u^2 \quad (14) \]

where \( A \) and \( B \) are proportional respectively to the membrane stretching and bending elastic constants and can be dependent on \( r \), but not on \( u; \Delta = \partial^2 / \partial x^2 + \partial^2 / \partial y^2 \) is the Laplace operator.

Combining Eqs. 11, 14 and 12 we find the spring constants:

\[ c_{ij}^{\alpha\beta} = (2 - \delta_{ij}) \int (B \Delta \phi_i^u \Delta \phi_j^u + A \phi_i^u \phi_j^u) df \quad (15) \]

### 3.2 Azimuthal variation of the contact slope

#### 3.2.1 General formulas

A possibility that the contact slope can become anisotropic at the contours of two interacting insertions was studied in [6]. The slope was presented as

\[ s_i(r_{\gamma_i}) = a_i + b_i f_i(r_{\gamma_i}) \quad (16) \]
where $a_i$ and $b_i$ do not depend on $r$, and $f_i(r)$ are the fixed functions. In practice, functions $f_i(r)$ approximate the azimuthal variation of the contact slope. If energy is minimized over the slope parameters $a_i$ and $b_i$, then different choices of $f_i(r)$ result in different families of trial functions $s_i(r)$. 

The surface displacement $u(r)$ can be expressed now through the boundary parameters $a_i$, $b_i$ and $u_i$.

$$u(r) = \sum_{i=1}^{N} [u_i \phi_i^a(r) + a_i \phi_i^b(r) + b_i \phi_i^c(r)]$$  \hspace{1cm} (17)

where $\phi_i^a(r)$ and $\phi_i^b(r)$ satisfy respectively the boundary conditions 4 and 10, while $\phi_i^c(r)$ satisfies the following conditions:

$$\phi_i^c(r)|_{\gamma_k} = 0, \quad \nabla \phi_i^c(r)|_{\gamma_k} = \delta_{ik} f_i(r_{\gamma_k})$$  \hspace{1cm} (18)

The energy is still described by Eq. 12 with the spring constants defined by Eq. 12; the additional summation is now performed over the repeated indexes $\alpha, \beta = (u, a, b)$. 

### 3.2.2 Applications for two insertions

We consider now two identical insertions. Due to possible fluctuations, parameters $u_i$, $a_i$, and $b_i$, and functions $f_i(r)$ for two insertions can still be different. The energy of two insertions is

$$E = c_{11}^{uu}(u_1^2 + u_2^2) + c_{11}^{aa}(a_1^2 + a_2^2) + c_{12}^{bb}(b_1^2 + b_2^2) + 2c_{11}^{ua}(u_1a_1 + u_2a_2) + 2c_{12}^{ub}(u_1b_1 + u_2b_2) + 2c_{12}^{ab}(a_1b_1 + a_2b_2) + c_{12}^{uu}(u_1u_2) + c_{12}^{aa}(a_1a_2) + c_{12}^{bb}(b_1b_2) + c_{12}^{ab}(u_1b_2 + u_2b_1) + c_{12}^{ab}(a_1b_2 + a_2b_1)$$  \hspace{1cm} (19)

where we used the symmetry conditions $c_{11}^{a\beta} = c_{22}^{a\beta}$, $c_{1j}^{a\beta} = c_{ji}^{a\beta} = c_{ij}^{a\beta}$.

We now consider symmetry conditions $c_{11}^{a\beta} = c_{22}^{a\beta}$, $c_{1j}^{a\beta} = c_{ji}^{a\beta} = c_{ij}^{a\beta}$. 

The allowed functions $f_i(r)$ should satisfy the condition $f_i(r) = f_i(-r)$, where $r = 0$ designates the midpoint between the insertions, with boundary parameters for both channels identical: $u_1 = u = u$, $a_1 = a_2 = a$, $b_1 = b_2 = b$. Then, the energy can be presented as

$$E = C_{uu}u^2 + C_{aa}a^2 + C_{bb}b^2 + C_{ua}ua + C_{ub}ub + C_{ab}ab$$  \hspace{1cm} (20)

where

$$C_{a\beta} = (2 - \delta_{a\beta})(2c_{11}^{a\beta} + c_{12}^{a\beta})$$  \hspace{1cm} (21)
Thus the total number of the effective spring constants is reduced to six. We intent to study the optimized ("relaxed", "equilibrium") slope, so that

$$\frac{\partial E}{\partial a} = 0, \quad \frac{\partial E}{\partial b} = 0$$  \hspace{1cm} (22)

These conditions lead to

$$a = \frac{2C_{bb}C_{ua} - C_{ab}C_{ub}}{\Delta}, \quad b = \frac{2C_{aa}C_{ub} - C_{ab}C_{ua}}{\Delta}, \quad \Delta = C_{ab}^2 - 4C_{aa}C_{bb}$$  \hspace{1cm} (23)

As a result, the total energy minimized over \(a\) and \(b\) can be written as

$$E_{\text{min}} = Ku^2$$  \hspace{1cm} (24)

$$K = \frac{C_{bb}(C_{aa}^2 - 4C_{aa}C_{uu}) + C_{ab}(C_{ab}C_{uu} - C_{ua}C_{ub}) + C_{aa}C_{ub}^2}{\Delta}$$  \hspace{1cm} (25)

We can now see that six effective spring constants \(C_{\alpha\beta}\) define the equilibrium slope parameters \(a\) and \(b\) and the equilibrium energy \(E_{\text{min}}\).

The effective spring constants can be found from Eq. 15. Sometimes, however, it is more practical to use the energy values \(E\{u, a, b\}\) defined for different sets \(\{u, a, b\}\) of the boundary parameters.

For every distance \(d\) between the insertions, the elastic energy \(E\{u, a, b\}\) can be calculated numerically [1]. Then, all six spring constants can be found. The following equations illustrate this approach:

$$C_{uu} = \frac{E\{u, 0, 0\}}{u^2}, \quad C_{aa} = \frac{E\{0, a, 0\}}{a^2}, \quad C_{bb} = \frac{E\{0, 0, b\}}{b^2},$$

$$C_{ua} = \frac{E\{u, a, 0\} - C_{uu}u^2 - C_{aa}a^2}{ua}; \quad C_{ub} = \frac{E\{u, 0, b\} - C_{uu}u^2 - C_{bb}b^2}{ub};$$

$$C_{ab} = \frac{E\{0, a, b\} - C_{aa}a^2 - C_{bb}b^2}{ab};$$

With these constants, the equilibrium (or minimized over the slope parameters) interaction energy profile \(E_{\text{min}}(d)\) can be determined from Eq. 21.

4 Final remarks

It was shown that interaction energy between the insertions can be described in terms of effective spring constants accounting for the coupling between various degrees of freedom introduced through the boundary conditions. After the spring constants are defined, the equilibrium slope (which can in general become anisotropic) and corresponding interaction energy can be defined analytically. This approach is much more efficient than the direct energy minimization used in [1]. Some applications of this approach will be considered elsewhere.
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