David Holcman · Zeev Schuss

Stochastic Narrow Escape in Molecular and Cellular Biology

Analysis and Applications

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Des petits trous, des petits trous, toujours des petits trous, S. Gainsbourg, le poinçonneur des lilas, 1958.

Preface

This monograph consists of two main parts, mathematical and biological. The mathematical part, which is quite sophisticated involving advanced asymptotic methods in partial differential equations, is aimed primarily at applied mathematicians and theoretical physicists who are interested in biological applications. The targeted readership of the second part is much wider and includes also computational biologists, theoretical chemists, biochemists, biophysicists, and physiologists. This part does not necessarily require the in-depth digesting of the tough analysis of the first part. It includes a summary of output formulas from the first part and mainly concentrates on their applications in various models of specific problems in theoretical molecular and cellular biology.

Stochastic narrow escape consists in the passage of a diffusing particle through a narrow opening in an impermeable wall or the arrival of the trajectory of a diffusion process at a small target. For example, a stochastic narrow escape occurs when an ion diffusing inside a biological cell finds a protein channel molecule embedded in the cell membrane and squeezes through it across the membrane. A similar situation occurs when a neurotransmitter molecule, such as glutamate, released from a vesicle at the pre-synaptic terminal into a synaptic cleft of a neuron, finds its way by diffusion to a receptor on the post-synaptic terminal of an excitatory synapse and binds to it. Another example is a channel, such as calcium, or a receptor, moving toward its destination in the post-synaptic density (PSD) on a cellular membrane crowded with insurmountable and impermeable obstacles, finds its destination by diffusion through the narrow openings between the obstacles.

The mathematical narrow escape problem in stochastic theory is to calculate the mean first passage time (MFPT) of a diffusion process to a small absorbing target (Dirichlet boundary) on the otherwise impermeable (Neumann) boundary of a bounded domain (see Fig. 1.1). The main mathematical effort here is to develop asymptotic methods for the approximate evaluation of the MFPT (also called the narrow escape time, NET) in the various geometries of cellular structures (see Sect. 3.3). The problem is equivalent to the construction of an asymptotic solution to the homogeneous mixed Neumann–Dirichlet boundary value problem for the Poisson equation in a bounded domain in the limit of shrinking Dirichlet part.

The NET becomes infinite in this limit, thus rendering its computation a singular perturbation problem.

We review in Chaps. 1–3 of this monograph recent developments in the non-standard asymptotics of the problem, which are based on several ingredients: a better resolution of the singularity of Neumann's function, resolution of the boundary layer near the small target by conformal mappings of domains with bottlenecks, and on the break up of composite domains into simpler compartments. The new methodology applies to two- and higher-dimensional problems.

In Chaps. 4–9, we review applications of the narrow escape problem in cell biology (see Holcman and Schuss 2013a,b). Critical biological processes, such as synaptic plasticity and transmission, activation of genes by transcription factors, or double-stranded DNA break repair, are controlled by diffusion in structures that have both large and small spatial scales. These may be small binding sites inside or on the surface of the cell, or narrow passages between subcellular compartments. The great disparity in spatial scales is the key to controlling cell function by structure. We report here recent progress on resolving analytical and numerical difficulties in extracting properties from experimental data, from biophysical models, and from Brownian dynamics simulations of diffusion in multi-scale structures.

The results of Chaps. 1–3 are applied first to the classification of the various geometries of cellular domains that control ionic and molecular fluxes. The different NETs in various cell geometries are manifested in Brownian dynamics simulations in cellular biology. Specifically, Brownian dynamics simulations can be coarse-grained to the time scale of the NET, thus revealing the dependence of cell function on cell structure.

The resolution of the synaptic transmission by solving the NET problem in the synaptic cleft and in the dendritic spine takes advantage of the particular geometries of the synaptic spine and of the synaptic cleft. The explicit asymptotic expression of the NET is applied to stochastic chemical reactions in microdomains, to regulation of calcium flux through the dendritic spine neck, to the delivery of vesicles in neurite outgrowth, to DNA repair in two-dimensional confinement, to control of reactions by hidden binding sites, to asymmetric dumbbell-shaped division in cells, to coarse-graining a stochastic model of a chemical reaction into a Markov chain model, to the coarse-graining of molecular diffusion on a membrane crowded with obstacles to an effective diffusion, as observed in supermicroscopic imaging, to physical virology with a model of the early steps of viral infection in cells, and so on.

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