Fusion between membranes is a ubiquitous cell biological process, occurring in a multitude of vital cellular events. The structure that joins two membranes, establishing continuity between their two formerly separate aqueous compartments, is the fusion pore; its formation and enlargement occur via a protein-mediated, multi-step process. Several critical intermediate steps of this process have been characterized experimentally. A number of theoretical models of membrane fusion have been developed, including continuum models that can cover the broad range of time scales over which steps of fusion occur. However, these classical continuum methods have assumed equilibrium and neglected energy dissipation, even though biological fusion requires external energy to overcome significant energy barriers, and considerable energy dissipates because both fusing membranes and their surrounding aqueous phases are viscous and moving. New mathematical methods now make it possible to overcome previous theoretical limitations. The modern continuum method of phase field accounts for energy dissipation; the string method finds the pathway of minimal energy over barriers. By making use of these new methods, we will mathematically obtain the most favored energetic pathway to reach each experimentally determined intermediate state of fusion. The transitions to each state are (1) the partial merger of separate membranes into hemifused ones; (2) the formation of the initial fusion pore in the single-bilayer structure termed a 'hemifusion diaphragm'; and (3) the growth of the initial pore to a size that permits passage of macromolecules. We will model each transition between states. The string and phase field methods will be combined to obtain pathways from separate to hemifused membranes, a process in which energy is biologically supplied by fusion proteins. It has been found experimentally that not all hemifused membranes form pores; membrane configurations therefore must be heterogeneous, but the causes of these biologically important heterogeneities remain completely unknown. We will investigate this problem mathematically by generating a multitude of initial hemifusion paths, determining the different hemifusion states that result, and finding the characteristics of those states that can proceed to pore formation. We will formulate a new model of a lipid bilayer membrane that will account for the topological changes required for a fusion pore to form within a hemifusion diaphragm by combining a phase field formalism for the interface between immiscible fluids with techniques used in liquid crystal theory. The model will, for the first time, mathematically describe a lipid bilayer as a thin, ordered, elastic material, rather than a surface of zero thickness. The geometry of the boundary between a hemifusion diaphragm and the two original membranes is not a surface, but instead is a singular set. We will therefore separately model pore formation in the interior of the diaphragm and at the boundary. For the interior, we will generate pores mathematically by increasing surface tension of the membrane, and follow the lipid rearrangements. We will use the equivalence between the geometry of the boundary and singular sets to develop a new formalism that connects finite elements into the geometry of the diaphragm boundary. Through this dual approach, we will calculate the energies needed to create a pore at the boundary and in the middle of a hemifusion diaphragm, and thereby locate the site that requires minimum energy. The topological changes during hemifusion and pore formation that characterize fusion will not be merely asserted, as has been done to date, but will be calculated outputs of mathematically well-defined models. The changes in minimal energy shapes that occur over the time course of fusion pore enlargement and the slowing of growth caused by frictional shear forces within the aqueous solutions have never before been considered mathematically; we will include both effects in our calculations and compare time courses to those obtained experimentally. **Intellectual Merit.** Our program will yield novel strategies for modeling deformations and topological changes in membrane fluid motion, lead to new applications of variational methods, develop original mathematical formalisms for describing the elastic properties of membranes, derive the long-sought lipid rearrangements of key steps of fusion, and reveal fundamental biological mechanisms that could not be investigated by prior theoretical approaches. **Broader Impacts.** Our teaching program introduces students of mathematics to areas of current cell research, and trains them in applying mathematical approaches to biological problems. Mentored undergraduates directly participate in modern research areas at the interface of mathematics and biology. All developed software will be freely shared to aid other theoretical scientific calculations in this important field of study.