The Molecular Logic Stepping Stones: The Molecular Logic project created a set of ten “Molecular Stepping Stones,” model-based activities, each focused on one of the basic physical-chemical principles underlying biological processes. The Stepping Stones build on each other in a logical sequence, roughly ordered from fundamental physical concepts, through chemistry and into molecular biology.

<u>The molecular Stepping Stone concepts, with examples of how students interact with the model in each activity</u>

Molecular Stepping Stone	Example of students’ interaction with the model
1. Random Motion	Trace the path of particles in Brownian motion
2. Diffusion, Osmosis and Equilibrium	Count particles that have moved across a membrane
3. Strong Chemical Bonds	Change electronegativities of atoms to create different types of covalent bonds
4. Compounds	Explore properties of macromolecules across the tree of life
5. Intermolecular Forces	Compare attractive forces between polar and non-polar molecules
6. Molecular Folding and Self-Assembly	Modify a protein’s primary structure and observe a change in folding
7. Structure and Function in Proteins	Explore a 3D molecular model to find and reason about structural features
8. Chemical Reactions and Catalysis	Modify bond strengths to create reactions with different properties
9. From Genetic Code to Protein Structure	Make a point mutation and observe its effects on the resulting protein
10. Genotype to Phenotype	Edit a genotype and observe resulting phenotype

One thread running through the stepping stone sequence is the idea of random motion at the atomic scale. The first stepping stone explores the idea that atoms and molecules are constantly moving, which is called Brownian motion. In this activity, students add particles into a model and observe their interactions with other particles. They learn that their random motion is a result of many collisions from all sides. Using the modeling tool, students experiment by increasing the temperature of the system to determine how heat affects molecular motion. Stepping stone two elaborates on the concept of random motion to explain diffusion and osmosis.

Another thread running through the sequence is weak intermolecular attractions. In stepping stone three, students learn about electronegativity, and how it results in different types of bonds: non-polar covalent, polar covalent, and ionic. Students are asked to reason about the polarity of water. In stepping stone four, they view a variety of 3D models of biomolecules, and see that many have polarized surfaces. In the fifth stepping stone, they explore the variety of weak attractions between molecules, including polar and non-polar attractions, and hydrogen bonds. In stepping stone six they can experiment with the role of these weak attractions in a two dimensional model of protein folding. Here they also experiment with self-assembly of monomers into larger molecular assemblies, combining weak electrostatic attractions with the random motion seen in earlier stepping stones. Thus from simple concepts of random motion and stickiness between particles, a more sophisticated view of the molecular world emerges. Armed with this understanding, students can take on an exploration of protein structure and function using 3D models (stepping stone 7), and experiment with chemical reaction models in the context of catalysis and enzymes (stepping stone 8).

The stepping stone sequence culminates with an exploration of the central dogma of molecular biology. In stepping stone 9, students work with a model that shows the entire process of protein synthesis, from DNA sequence, transcription, translation to protein folding. They can edit the DNA sequence, for example to create a frame shifting insertion mutation, and observe the dramatic effects on the shape of the resulting protein, driven by the molecular motion and interactions they've seen throughout the stepping stones. Finally in stepping stone 10 students can try out a model of heredity that draws on the molecular view in connecting genotype to phenotype.