Evolutionary design of a DDPD model of ligation

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Abstract. Ligation is a form of chemical self-assembly that involves dynamic formation of strong covalent bonds in the presence of weak associative forces. We study an extremely simple form of ligation by means of a dissipative particle dynamics (DPD) model extended to include the dynamic making and breaking of strong bonds, which we term dynamically bonding dissipative particle dynamics (DDPD). Then we use a chemical genetic algorithm (CGA) to optimize the model's parameters to achieve a limited form of ligation of trimers—a proof of principle for the evolutionary design of self-assembling chemical systems.

1 Evolutionary design of self-assembling chemical systems

Many familiar examples of supramolecular self-assembly—such as micelles and vesicles—result solely from the dynamics of weak associative forces between molecules. Such structures contain strong intramolecular covalent bonds that are relatively fixed during the self-assembly process. Here we consider the self-assembly of supramolecular structures formed through the dynamics of strong bond formation in the presence of weak associative forces. Specifically, we focus on the self-assembly that occurs during monomer to polymer ligation, as part of the process of complementary templating. During the ligation process, weak associative forces enable the template to act as a physical catalyst for the construction of the complementary polymer's strong bonds. We study templating partly because it is critical in the growth, reproduction, and evolution of all contemporary biological life, but mainly because it is one of the simplest forms of molecular self-assembly that involves the dynamics of both strong bonds and

weak associative forces. In addition this process results in the replication and transfer of chemical information.

Evolution in nature has created exquisite chemical systems for ligation. All fundamental processes in the cell such as DNA replication, transcription and translation are based upon template-directed ligation of monomers. Our goal here is to create an artificial evolutionary process that designs a chemical system that achieves a simple analog of ligation. Other kinds of artificial evolutionary processes have been used for chemical design; in particular, "directed" or "in vitro" evolution has been used to design molecules with specific desired functionality [1–7]. But our evolutionary design procedure is different from directed evolution in two crucial respects. First, rather than evolving a population of molecules (e.g., RNA) for a specific function, we evolve the experimental parameters that describe a complete chemical system or process. While directed evolution aims to optimize individual functional molecules, our procedure aims to optimize whole chemical systems or processes containing a number of chemical species engaged in myriad chemical reactions. Second, directed evolution involves chemical systems that contain molecules encoding the information that is evolving. By contrast, in our method the information that is evolving is encoded outside the chemical system (in an experimenter's lab notebook or inside a computer). Thus, our method can be applied to design virtually any kind of chemical system or process.

The work reported here concerns the evolutionary design of a chemical model, not a real chemical system. However, this is not a limitation of our method. The same method could be used to design real self-assembling chemical systems, ultimately including quite complex systems like artificial cells that involve the integration of different chemical systems for containment, metabolism, and genetics [8]. As it happens, the chemical systems we optimize here are analogous to the chemical system of non-enzymatic template-directed synthesis [9–15]. Like template-directed systems of ligation *in vivo* and *in vitro*, our system is supplied with a template molecule and an excess of monomers. It then evolves so as to optimize the assembly of monomers on the template to produce a ligated copy of the template. In Section 2 we describe our dynamic-bonding dissipative particle dynamics (DDPD) chemical model. A description of the chemical genetic algorithm (CGA) used to design chemical systems follows in Section 3. The results of applying the chemical genetic algorithm to DDPD models that achieve a simple form of ligation are presented and discussed in Section 4, followed in Section 5 by a discussion of the proper design of CGAs and their practical limitations. We conclude in Section 6 with a discussion of some different kinds of dynamics in evolutionary design or "programming" of chemical systems.

2 Dynamic-bonding dissipative particle dynamics (DDPD)

Our model of chemical reaction systems is based on the well-studied dissipative particle dynamics (DPD) framework [16–21]. The DPD framework is a meso-

scopic system simulator meant to bridge the gap between molecular dynamics (MD) models and continuous substance models. The extreme computational demands of MD models make them appropriate only for simulating small systems for brief intervals—orders of magnitude smaller than the time and length scales of interest here. Continuous substance models are inappropriate as models of molecular scale systems in which the discrete nature of particles impacts the dynamics of the system.

In DPD, the equations of motion are second order, with explicit conservation of momentum, in contrast to Langevin or Brownian dynamics. Solvent molecules may be represented explicitly, but random and dissipative forces are included in the dynamics to compensate for the dynamical effects of replacing the hard short-range potentials of MD by softer potentials in DPD simulations. This procedure allows a major accelaration of the simulation compared with MD.

Our work is based on a DPD implementation of a model of monomers and polymers in water. Some elements in the model represent bulk water (one model element representing many molecules). Other elements could represent hydrophilic or hydrophobic monomers. In some cases those elements are connected by explicit bonds, which are represented as springs that freely rotate about their ends. These complexes explicitly but very abstractly represent the three-dimensional structure of polymers. For example, amphiphilic molecules can be created by explicitly bonding a hydrophilic monomer "head" onto a hydrophobic "tail" (chain of hydrophobic monomers).

All the elements move in a two- or three-dimensional continuous space, according to the influences of four forces. A conservative force governs symmetric pairwise repulsion and attraction of elements. A dissipative force causes the kinetic energy of elements to move towards equilibrium with other elements in the region. A random force imparts kinetic energy to the elements in arbitrary directions. The strength of the random force is calibrated to balance the lessening of system energy due to the dissipative force, maintaining the temperature of the system around a more or less fixed point. All of these forces are considered to operate only within a certain local cutoff radius. The cutoff radius is a main mechanism for improving model feasibility. Elements which are strongly bonded to other elements are also influenced by the movement of those elements to which they are bonded, through the spring that connects them.

The DPD framework supports two distinct types of particle interaction. The first type of particle interaction is referred to as "strong bonds," which represent covalent chemical bonds. All strong bonds in DPD are specified initially, and subsequently cannot form or break. Strong bonds are modeled by a Hooke's law spring. One limitation imposed on the DPD simulations discussed here is that each element can have at most two strong bonds at a given time. The second type of particle interaction corresponds to weak forces such as van der Waals forces or hydrogen bonds. Weak interactions are modeled by the Lenard-Jones potential, with different parameter values possible for interactions between different particle types. In contrast to real systems, attractive forces are not limited to a pair of elements, but may simultaneously occur between a single

element and many others. Orientation of individual elements also plays no role, as DPD elements are completely symmetrical. Thus, the pairing that occurs is a cooperative phenomenon.

DPD thermodynamic forces can create self-assembled structures held together with the weak associative forces. For example, a DPD system with amphiphiles in water can exhibit a wide variety of the known supramolecular amphiphilic phases, including monolayers, bilayers, micelles, rods, vesicles, and bicontinuous cubic structures [19, 22–25].

We augment the DPD framework by making strong bonds dynamic. This dynamic-bonding DPD (or DDPD) is a DPD that is augmented with the following two rules:

- Bonds form (with probability 1) if elements are within the bond-forming radius.
- Bonds break (with probability 1) if bonded elements are outside the bond-breaking radius.

The strong bond strength parameter governs the strength of all strong bonds, whether or not they were present in the initial conditions. An obvious generalization is to allow lower probabilities in the two bonding rules.

Note that the temperature of the system changes when bonds form and break. However, the momentum in the system is constant, since the changes in the momentum of individual elements due to bonding events are always symmetrical with respect to the bonded particles.

Chemical amplification via templating is the basic mechanism of DNA replication, and also of simpler replicator systems such as von Kiedrowski's autocatalytic replicator system [26] and peptide replicators [27]. Monomers of a given type may participate in a weak interaction with monomers of a complementary type, and each may form strong bonds with a monomer of any type if the two are in the correct proximity and orientation. Given a template polymer made up of different types of units and a reservoir of free floating monomers, each unit of the template polymer can associate weakly with a complementary monomer. When and if the weak forces bring the units into the correct orientation and proximity with complementary units in the template polymer, strong bonds form between the monomer units producing a complementary polymer through the process of ligation.

If the paired complementary polymers are separated by a mechanism such as duplex melting due to temperature change or protein action, then each polymer may repeat the process, creating more templates and complements. By this means, the overall number of polymers in the population increases. Although this process results in the chemical amplification of polymers, the focus of the present work is simply ligation, and the optimization of parameters that result in the organization and ligation of monomers into polymers.

To keep the chemical system as simple as possible, we focus solely on the ligation of two types of monomers into trimers, and we prevent strong bonds from breaking. Pairs of opposite type units attract each other, while like type units

are unlikely to become associated by weak forces, which is roughly analogous to complementary base pairing in the context of nucleotides.

We do not report here a complete analysis on catalytic efficiency of the templating process, with fitting of rate constants and comparison with background rates. Such analysis will be reported in future work.

3 Chemical genetic algorithm (CGA)

We now describe a "chemical genetic algorithm" (CGA) for designing chemical systems. We use the CGA to optimize the parameters of a DDPD model of ligation. The CGA could equally well be used to optimize parameters for other models, or for other chemical systems, or for other systems in general.[7]

The search space of our CGA is a subset of DDPD parameters. In particular, our genes are five chemical system parameters: (i) the strength of the attractive conservative force between complementary particle types, (ii and iii) the strength of the repulsive conservative force between the two types of like particles, (iv) the bond-forming radius, and (v) the bond strength. In the context of this paper, a genome is always a set of these five chemical systems parameters.

The CGA search procedure starts by measuring the fitness of the genomes that form the first generation. Then the following loop is repeated until the experiment ends: The most recently produced instance of the most fit genome is used to create a subsequent generation of genomes, by mutations of the five genome parameters. These mutations are governed by a global mutation rate, which acts within a range and style of variation defined for each parameter. A candidate mutated genome is included in a subsequent generation only if it differs from each genome tested in any previous generation. Then the fitness of each genome in the new generation is measured.

A genome's fitness is measured by starting the DDPD with the genome's parameters and seeding the system with free monomers and template trimers. No complementary trimers are included initially. The fitness of a genome is the number of complementary trimers formed after a globally fixed number of model updates. Many generalizations and modifications of our search algorithm and fitness function could be explored.

4 Results of evolutionary design of a ligation model

We used the CGA to design chemical systems for complementary-bonding ligation dozens of times, all with roughly the same results. Figure 1 shows the time

[7] It is worth noting that our chemical genetic algorithm differs from another algorithm devised by H. Suzuki that has been given the same name [28]. Inspired by metabolic reactions of molecules responsible for the biological translation of genetic information, Suzuki's algorithm is an unusual genetic algorithm that includes analogues of a cell containing tRNAs, amino acids, and aminoacyl-tRNAs, as well as DNA. Our CGA, by contrast, is a ordinary genetic algorithm, but one that is applied to the problem of designing optimal chemical systems.

series of the fitness and allele values of the most fit chemical system in a typical CGA run in this series. The fitness increases over time, in fits and starts (common with genetic algorithms), and the allele values in the genome of the most fit system change with each fitness increase.

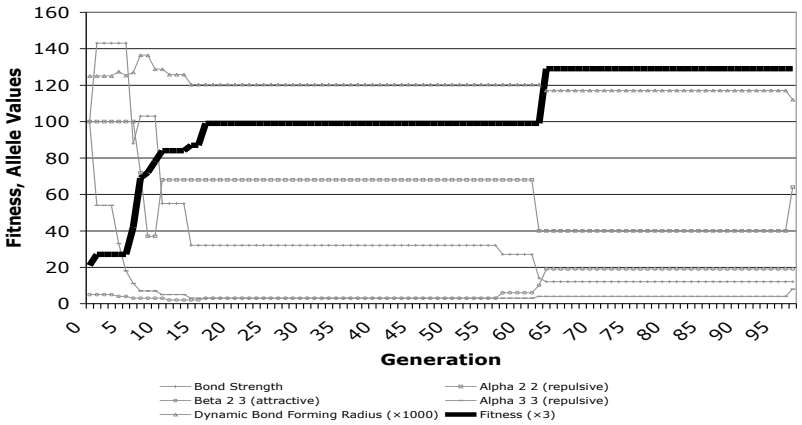

Fig. 1. A time series of the fitness (bold line) and allele values of the most fit chemical system in each generation of a typical CGA run. This shows the lineage of the most fit genomes through five-dimensional parameter space, indicating which allele (model parameter) changes correspond to each fitness increase. Fitness and many model parameters are scaled to improve visualization. Note that fitness increases overall.

Figure 2 shows the genealogical tree of each chemical system generated in the same CGA run. It vividly shows how the operation of the CGA allows only those measured as most fit to be parents. The top line of the genealogy corresponds to the lineage of the final optimal genome designed by the CGA.

Figure 3 again shows the maximum fitness in Figure 1, but now superimposed with twenty fitness measurements of some of the most fit systems. Each scatter plot was created by rerunning the DDPD parameters with twenty different random initial conditions. As might have been expected, the scatter reveals significant noise in our fitness measurements.

Figure 3 supports two conclusions. First, the overall increase in average fitness shows that the CGA is genuinely creating chemical systems with significantly better fitness. In other words, the CGA works as desired; this holds in general when we have used the CGA to program ligation systems. Second, increases in *measured* fitness do not always correspond to increases in *actual* fitness, because of noise in the fitness measurements, e.g., an initial configuration that creates an unusually large number of complementary trimers.

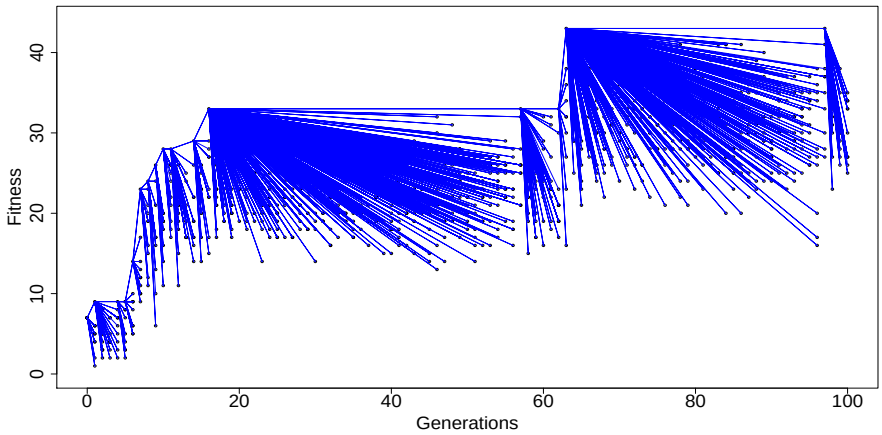

Fig. 2. A genealogical tree of each chemical system tested by the same CGA run shown in Figure 1. The generation of each system is indicated on the x axis, and its fitness on the y axis. Diagonal lines indicate parentage. Note that a parent is often not in the generation immediately preceding its children. Multiple systems in a given generation with the same fitness are shown as one point.

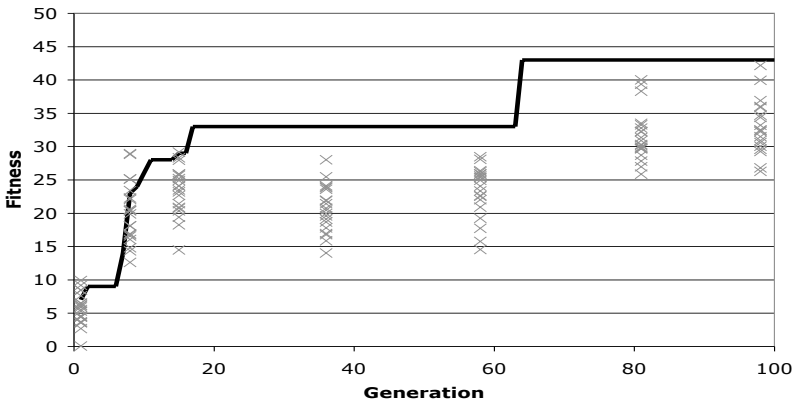

Fig. 3. A time series of the fitness of the most fit chemical system in each generation of the CGA run shown in Figures 1 and 2, overlaid with scatter plots of twenty fitness evaluations of some of those systems (with some random noise added, to distinguish identical fitness values). As expected, the fitness of the most fit is sometimes higher than any of the fitness values in the corresponding 20-value scatter plot, because the CGA generates many more than 20 trials.

5 Chemical genetic algorithm design

Proper design of a CGA involves confronting trade-offs between the accuracy of fitness measurements and the evolutionary design time scale. More accurate measurements are always possible, but they take more time. The number of different systems that a CGA can evaluate is strongly limited by available time and technology. At the same time, the effectiveness of a CGA is limited by the accuracy of its fitness measurements.

5.1 Noise in fitness measurements

The true fitness of a genome that describes the parameters of a given chemical system is the system's propensity to produce templating reactions under a variety of initial conditions. The fitness function actually used here, however, is the number of complementary templates formed starting from a single random initial configuration. Specific attention is not given to how the complements were formed, what other chemical species were formed, or how many might form under different initial conditions. The scatter in Figure 3 shows that this is an imperfect measure of actual templating propensity. The noisiness of our fitness measurements strongly depends on the chemical system's experimental parameters, whether or not they are in the genome.

In general, the noisiness of each fitness function must be measured empirically. We could do this by applying the fitness function to a single genome in a variety of contexts, by varying such things as the number of model updates, U, used in one fitness measurement, the system size, S, and the initial density of monomers, M. The noisiness of each point in $U \times S \times M$ space could be measured with a scatter plot.

Any GA, including the CGA, can function properly only given sufficiently accurate fitness measurements. One could more accurately assess fitness by averaging repeated fitness measurements under different initial conditions, but this takes substantially more time. To ensure both proper CGA function and optimal CGA design speed, one should make the minimum number of fitness measurements necessary for the requisite level of significance in measured fitness. This raises a precise statistical question: How many fitness measurements are required to get an accurate enough measurement that the CGA can continually find better model parameters?

Fixing the values of all the simulation parameters and then repeating the simulation from different random seeds n times, one obtains n values of the fitness function, $X_1, \ldots, X_n$. Clearly, these variables are independent and identically distributed. The distribution of these variables depends on the details of the simulation, which depend on the parameters that govern the simulation, including U, S, and M, as well as the parameters encoded by the genome. Assume for the moment that this distribution is roughly approximated by a normal distribution. Then we could infer the mean value, μ, of the fitness function for n repetitions by means of standard confidence interval estimation techniques

based on the t-distribution for the pivotal quantity $\frac{\sqrt{n}(\bar{x}-\mu)}{\hat{\sigma}}$, where $\bar{x}$ is the sample mean and $\hat{\sigma}$ is the estimate of the standard deviation. This would permit us to determine a sample size necessary to obtain an arbitrary desired accuracy, A. For a 95 percent confidence interval we can in fact derive from $A = \pm t_{n-1;0.025}\frac{\hat{\sigma}}{\sqrt{n}}$ the smallest sample size that leads to the desired accuracy.

This would permit us to determine a sample size necessary to obtain an arbitrary desired accuracy in estimated mean fitness, given the parameter values. Of course, one would have to validate empirically whether the variation in fitness measurements is well approximated by a normal distribution. If not, through an analysis of the simulation process, one could derive a better approximation of this distribution and base the sample size calculation on this approximation.

5.2 Chemical design time scales

The present discussion of time scales for simulation are based on use of a Macintosh Dual 2 GHz PowerPC with no parallelization (single-threaded code). The algorithm was not particularly optimized, but performs at speeds comparable to other DPD research codes on benchmark problems.

The running time of a CGA depends on the following numbers (with values for the present CGA results in parentheses):

- seconds per model update (10^{-1})
- model updates per fitness evaluation ($10^2 - 10^3$)
- systems evaluated ($10^3 - 10^5$)

Combining these numbers shows that each CGA run takes between $10^4 - 10^7$ seconds, that is, between hours and months. This spans the range of experiments worth and not worth attempting. Furthermore, we saw above that successful CGA operation might require averaging repeated fitness measurements before estimating a chemical system's actual fitness. Such repeated measurements would increase the running time of the CGA by an order of magnitude.

Thus, the time feasibility of our CGA designing DDPD parameters critically depends on the number of model updates required for each fitness evaluation and the accuracy of the evaluation. For example, the spontaneous self-assembly of vesicles in the DPD framework typically takes on the order of a week of user time, so the fitness function for a CGA designing vesicles would probably require about the same amount of time. Hence, the CGA would take years to evaluate the fitness of even hundreds of systems—which is clearly beyond the bounds of human patience.

We conclude by noting that the execution times discussed here may be significantly improved by hardware and clever coding, as well as DDPD enhancements that lead to more complex particle interaction primitives. On the other hand, full simulation of dissociation at thermal equilibrium could increase execution times.

6 Dynamics of evolutionary design of chemical systems

One can distinguish three kinds of dynamics involved in the evolutionary design of chemical systems. First, the DDPD model involves the dynamic of chemical species. This dynamic takes place in a continuous two- or three-dimensional space supporting spontaneous self-assembly processes. Bonds form and break; the concentrations of chemical species rise and fall; new species are created; old species go extinct. DDPD models achieve these dynamics by the addition of dynamic strong bonds.

The evolutionary design of DDPD parameters sufficient for ligation of trimer templates is a step toward a second kind of dynamic—evolution of informational polymers by natural or artificial selection. Modeling the evolution of informational polymers is a burgeoning field. The focus on the line of work presented here is a model in which the polymer evolution is produced by catalytic activity physically embodied in explicit spatial structures—an example of what could be called "embodied information processing."

The chemical GA itself is a proof of principle for a third kind of dynamic, specifically, the evolutionary design of a chemical system with prespecified functional properties. The scheme used here for the evolutionary design of chemical model parameters for ligation could be used to design model parameters for different self-assembled structures, such as micelles or lamellar sheets. The scheme could also be used to design the parameters of other kinds of models entirely. If those models are realistic, then the evolved model parameters could be used to design real chemical systems. The CGA can also be used to design real chemical systems directly, such as those that produce some desired kind of self-assembled structures. Designing a CGA to produce a specific kind of self-assembled system is a method for "programming" such systems.

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Appendix. The DDPD parameters in the work reported here were as follows: The conservative force between particles i and j was given by an approximation of the Lennard-Jones potential $F_{ij}^{C} = \alpha(\frac{1}{r_{ij}^{y}} - \frac{\beta}{r_{ij}^{z}})$, where α is the maximum repulsive force, β is the factor for the attractive force, r_{ij} is the distance between the particles, and y and z are parameters governing the level of approximation. α was initially set to 100 and allowed to vary between 1 and 100 for like type interactions, while β was fixed at 1. For interactions between unlike types α was fixed at 1 and β allowed to vary between 1 and 100, being initially set to 5. In

interactions with the "water" particle type, both α and β were fixed at 1. For all particle interactions, y was set to 0 and x to -1.

Every DDPD simulation ran for 500 iterations. The scaling factor for the dissipative and random forces, σ, was 3. The independent scaling factor for the random force was 1.73205 ($\sqrt{3}$). The integration interval, dt, was 0.01. The spring constant governing forces between bonded particles varied between 10 and 400, being initially set to 100. The minimal energy length for bonds was 0.01. The system was a 10 by 10 square initialized with 700 "water" particles, 90 free type-one particles, 180 free type-two particles and 10 chains of two type-one particles followed by a type-two, 1000 total particles, all randomly placed. The dynamic bond forming radius was chosen from 0.1 to 0.5 with a starting value of 0.125. Bonds were not dynamically broken, loops were not allowed to form, and the maximum length for dynamically formed polymers was fixed at 3. Dynamic bonds were allowed to form only between like particles of type-one or -two, and between type-one and type-two particles.

In the CGA, every generation consisted of 10 DDPD parameter files based on the parameter file with the highest fitness to that point, or the more recent file in case of ties. The five parameters that varied did so each with a mutation probability of 0.5. If mutated, the dynamic bond forming radius was chosen at random from $\pm$ 10% of the parent parameter. The range for all the other parameters was half to double the parent value.

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