Optimizing ring assembly: the strength of weak bonds

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***Short Abstract* — Most cellular processes rely on the assembly of large macromolecular complexes many of which contain ring-like structures (e.g. the proteasome and AAA+ ATPases). Using mathematical models we expose problems that are endemic to the assembly of rings. If all the subunits in a ring bind to one another too strongly, assembly times are significantly delayed due to deadlocks. If interactions are too weak, assembly delays are caused by the instability of intermediates. We demonstrate that rings containing at least one weak interaction assemble efficiently and robustly. Analysis of solved structures of ring-like complexes indicates they generally exhibit at least one weak bond.**

***Keywords* — Protein Interaction Networks, Self-assembly**

I. Introduction

LARGE complexes—consisting of multiple protein subunits that must assemble into a well-defined quaternary structure in order to function—are involved in many cellular processes [1,2]. A number of well-known examples of such complexes, including the proteasome, contain ring-like structures [2]. Indeed, rings may represent a kind of common structural "motif" in large complexes, perhaps due to their inherent stability [3] and symmetry.

In this work we explore the assembly dynamics of rings as a general class. This allows us to expose problems that are universal to the assembly of rings and understand how cells might have solved these problems over the course of evolution.

II. Results

The fundamental observation we have made is that the dynamics of ring assembly is characterized by a "deadlocked plateau" phase when the molecular interactions between subunits in the ring are too strong. In this case, smaller intermediates are consumed by the system *before* all of the rings have formed. Since large intermediates cannot productively interact with one another, the system must wait until these large intermediates dissociate; these dissociation events eventually allow assembly to proceed to completion.

If all of the bonds along the ring are constrained to have the same strength, we find that there is an affinity that minimizes assembly time. This optimal bond strength depends heavily on concentration; as concentrations increase, the affinity that characterizes minimal assembly time decreases. We have also found that this kinetic affect has a strong influence on assembly yields in models that consider the synthesis and degradation of subunits and intermediates.

In heteromeric rings, bond strengths need not be identical along the ring. We have found that including at least one bond in the structure that is weaker than the others produces a ring that will assemble very efficiently across a wide variety of total subunit concentrations. Such configurations also produce maximal yields in models containing synthesis and degradation.

To test whether living systems employ weak bonds to overcome assembly deadlocks, we considered all of the solved structures of heteromeric 3-membered rings in the PDB [4]. Using buried hydrophobic surface area as a rough proxy for bond strength [5], we found that such structures consistently contained at least one bond that was weaker than the others. This result suggests that optimizing assembly dynamics and yield has played a pivotal role in the evolution of bond strengths in ring-like complexes.

III. Conclusion

The assembly of large complexes is crucial to the function of living systems. Using a simple mathematical model, we have uncovered a fundamental problem that rings must face if they are to self-assemble efficiently. Our models suggest simple biophysical techniques that can be employed to overcome this problem, and we have provided evidence that evolution has produced ring-like structures that employ these techniques. Our work provides a basis for understanding the self-assembly of more complex structures, such as the stacked rings found in the proteasome [2].

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