

## Chemistry 430 — Simulation in Chemistry & Biochemistry

### Take-Home Final Examination — Spring 2019

**Answer the two questions below.** Please submit your responses as either a printed copy or PDF document file sent to Jay Ponder (drop off at Louderman 453 or email to ponder@dasher.wustl.edu) by the end of the last day of final exams, May 8th. The references cited below are provided on the course web site. You should use these papers as a starting point for discussion, but feel free to do your own literature searches and include information from other sources in your answers. In particular, there are review articles that overlap the topic of each question, and these may be easier to understand than the primary research articles.

You should provide intuitive explanations of the theory and main features in response to each question. While it is highly recommended to include various key equations in your answers, no detailed derivations or calculations are required. A complete answer for each question should be only a page or two in length.

**Question 1:** Peter Gill is a well-known quantum chemist. Born in New Zealand, he trained with Nobel Prize winner John Pople and was on the faculty at the University of Cambridge, prior to returning down under to a chair in Theoretical Quantum Chemistry at Australian National University. Along with Martin Head-Gordon (Chemistry, UC Berkeley), Gill founded Q-Chem, Inc., which produces a widely used software program of the same name that serves as the computational engine for Wavefunction's Spartan, among other uses. [Both articles referenced below are on the course web site under Readings: Density Functional Theory.]

(A) Unlike typical computational chemists, Peter Gill is an extremely witty and entertaining fellow. In 2001 Gill belatedly published "*Obituary: Density Functional Theory (1927-1993)*" in the *Australian Journal of Chemistry* (vol. 54, no. 11, pages 661-662). Explain the research reported in 1927 and in 1993 that led him to date the "birth" and "death" of DFT in those years. Outline major advances that have occurred in DFT since the obituary was published. In your opinion, to paraphrase Mark Twain, has the death of DFT been greatly exaggerated?

(B) In Gill's review for the *Encyclopedia of Computational Chemistry*, entitled "*Density Functional Theory (DFT), Hartree-Fock (HF), and the Self-Consistent Field*", he attempts to provide a unified derivation and discussion of both HF and DFT calculations. Using Gill's formulation and appropriate equations from his review, briefly explain the components of the HF energy (equation 21) and the B3LYP DFT energy (equation 28).

**Question 2:** We discussed various “search” and “sampling” methods in various parts of the course. Two classic methods we did not directly cover are temperature replica exchange molecular dynamics (T-REMD) and metadynamics. In 2015, Zerze, *et al.* compared T-REMD against a particular metadynamics-based method (so-called bias exchange metadynamics, BEMD) for exploration of the energy surface of an intrinsically disordered protein (IDP). IDPs are proteins that are largely unfolded under physiological conditions, and understanding their biological importance is a very active current research topic.

<b>T-REMD</b>	Sugita and Okamoto, <i>Chem. Phys. Lett.</i> , <b>314</b> , 141 (1999)
<b>Metadynamics</b>	Laio and Parrinello, <i>PNAS</i> , <b>99</b> , 12562 (2002)
<b>BEMD</b>	Piana and Laio, <i>J. Phys, Chem. B</i> , <b>111</b> , 4553 (2007)

**T-REMD and BEMD applied to IDPs**      Zerze, *et al.*, *JCTC*, **11**, 2776 (2015)

Briefly explain the basic methodology underlying the T-REMD and the original metadynamics methods. How does BEMD differ from the original metadynamics formulation of Laio and Parrinello? How do the two methods studied by Zerze, *et al.*, T-REMD and BEMD, perform for the IDP application?