This is Al Hero's and Jeff Fessler's section to the DARPA MOSAIC proposal.

1 Algorithms for Control and Image Reconstruction

The algorithm development and analysis team, led by Profs. Fessler and Hero, will be involved in many aspects of instrument control, image processing, and image analysis. In particular we will use suitable mathematical models to predict imaging performance, develop subsurface reconstruction algorithms, register multiple position scans, correct for probe-array cross-talk, and develop feedback algorithms for adaptive control of the probe-tip array.

In the description below we focus on algorithms applicable to an array of thermal probe tips whose z-positions are individually controllable. If time permits, we will also explore control and image reconstruction issues for: 1) piezo-electric probe tips; and 2) tandem-tip probes having tips mounted on a single rigid z-controllable platform. Such a system would be a cheaper and mechanically simpler design which would allow for more densely packed tips having the potential of higher spatial resolution. The height of the platform would be controlled to maintain a constant average force over all tips, resulting in a measurement from which the individually controlled array measurements would be demultiplexed from the measurements using signal processing.

1.1 Active Probe Control

Adaptive feedback control will be crucial for maximizing accuracy of the proposed constant-force multiple-probe AFM system. The adaptive model-reference control framework described below will lead to great improvements in image resolution by feeding back partially extracted information about the sample surface and subsurface structures in real time as the scan progresses.

For a multiple probe system the control of z motion of individual microtubes in the array properly falls in the domain of adaptive control of multiple-input-multiple output (MIMO) systems [7, 6], also called multivariable systems [5]. While one could certainly apply existing single-probe feedback control to each individual probe in the array this would be suboptimal since error signals from different probe tips are necessarily coupled due to their close proximity and the partial overalap of array at successive scan positions. Indeed, significant gains can in tracking accuracy can be obtained by treating the full MIMO control problem, see for example Zhou and Doyle [9, Ch. 8] for practical illustration. We will use the full power of adaptive MIMO control and signal processing methodologies for extracting the highest possible resolution from the probe array. In the context of the cantilever array the controllers will be based on a general recursion defining the time sequence of applied vertical displacement vectors $\mathbf{z}_k = [z_{1k}, \ldots, z_{pk}]^T$ (p is the number of individually controllable probe tips) of the form:

$$\mathbf{z}_k = \mathbf{A}\mathbf{z}_{k-1} + K_k \mathbf{e}_k$$

where $\mathbf{z}_k$ is the applied vertical displacement, $\mathbf{A}$ is a square matrix which accounts for temporal dynamics and cross-talk between probes, $\mathbf{e}_k = \mathbf{f}_k - c\mathbf{1}$ is the error signal consisting of the measured force vector $\mathbf{f}_k = [f_{1k}, \ldots, f_{pk}]^T$ and the constant force vector $c\mathbf{1} = [c, \ldots, c]^T$, and K_k is a gain matrix.

Adaptive model-reference controllers can further improve tracking accuracy when the measured force signal vector $\mathbf{f}_k$ can be represented by a state space dynamical model which accounts surface smoothness or gross structure available from previous scans:

$$\begin{aligned} \mathbf{f}_k &= \mathbf{C}\mathbf{x}_k + \mathbf{v}_k \\ \mathbf{x}_{k+1} &= \Phi\mathbf{x}_k + \Gamma\mathbf{w}_k. \end{aligned}$$

Where $\mathbf{v}_k, \mathbf{w}_k$ are additive noises and $\mathbf{x}_k$ is a state vector, e.g. related to subsurface structures, and $\mathbf{C}$ is a matrix which translates the state vector to atomic forces on the cantilevers. The simplest case to be considered is the case of a static non-time varying sample for which $\Phi = \Gamma = 0$. The more general case will allow us to factor in cell motion and interactions between probe and sample. This framework allows us to effectively couple image formation and reconstruction into the controller for resolution enhancement.

1.2 Subsurface Imaging

Thermal imaging using scanning micromachined thermal probes has recently shown increasing potential [10, 11, 12, 13]. The addition of an array of thermal probes offers additional 3D information on the biological sample which can be used to detect phase changes and other aspects of cell metabolism going on in the sample. As discussed above, such information could also be incorporated into the control loop to improve force tracking accuracy of the AFM. Particularly intriguing is the use of active thermal sources for subsurface measurements [14, 15, 16], sometimes called thermal wave imaging [17].

To perform accurate detection we will use mathematical models for thermal transport within the sample and to the probe tips by Gianchandani and Najafi [14]. Such models have been applied to non-biological samples, e.g. for non-destructive testing via scanning thermal microscopy where they have been used to implement inverse scattering solutions of the spatial thermal conductivity distribution (e.g. Gomez [4] and Seidel *etal* [8]). However previous models have several limitations for thermal imaging of biological samples that we will overcome. First, the models will be extended to accomodate internal heat sources. Second, the models will be extended to arrays of thermal probes. Third, the surface information provided by the AFM will be used to improve the inverse scattering solution. Fourth, the noise statistics of the probe and electronics which degrade the measurements will be explicitly taken into account. Accounting for characteristics of the noise distribution, has led to significantly improved imaging algorithms developed by co-PI's Fessler and Hero [3, 1] for 2D and 3D tomographic imaging and image restoration problems for PET, MRI, CT and other imaging modalities. Similar improvements can be expected for the scanning microscopes proposed here. These will not be not trivial extensions but they are feasible.

1.3 Image Reconstruction Methods

We propose to enhance the utility of thermal and atomic force measurements by developing, implementing, evaluating, and analyzing physics-based image reconstruction methods suitable for the measurement devices developed in this project. Our team has extensive experience in developing image formation methods based on accurate physical and statistical models, with experience in PET, SPECT, X-ray CT, MRI, and confocal microscopy. The general framework for addressing such inverse problems is well established, e.g., [18]. First one identifies an appropriate physical model for the forward problem, including as many relevent effects as possible. Then one identifies appropriate statistical model based on the measurement device properties, e.g., [14] in the case of scanning thermal profilers. The statistical log-likelihood associated with the physical model and statistical model is augmented with a regularization term to control the inevitable tradeoff between spatial resolution and noise. Finally, iterative algorithms are developed that rapidly converge to the minimizer of the overall cost function to produce the final reconstructed image, e.g., [19, 20]. Often multiple imaging modalities are available that provide complementary but partially correlated information, such as the topographic and thermal measurements in this project. We propose to extend our previous work on multi-modality image reconstruction, e.g., [21, 22, 23] to maximize the quality of image formation in this project.

1.3.1 Mathematical Methodology

Our subsurface reconstruction methods will be based on fast algorithms for solving statistical inverse problems that we have developed in the context of optical microscopy, and CT/PET medical imaging [2, 3, 1]. Subsurface reconstruction can be formulated as a statistical inverse problem by discretizing the sample into small 3D voxels and assuming a linear model for the sequence $\{\mathbf{Y}_k\}$ of observation vectors (e.g. cantilever position or measured temperature over time and space extent of the scanning array)

$$\mathbf{Y}_k = \mathbf{F}\mathbf{X}_k + \mathbf{N}_k, \tag{1}$$

as a function of the unknown vector $\mathbf{X}_k$ of coefficients, e.g. thermal conductivity over the voxels of the 3D sample, which are of interest. The matrix $\mathbf{F}$ is the system transfer function which depends on the underlying thermal transport of the medium and on physical properties of the probe. The residual modeling noise $\mathbf{N}_k$ accounts for mismodeling error and the variance of the vector of noises $\mathbf{N}_k$ may be dependent on the variance of $\mathbf{F}\mathbf{X}_k$, e.g. for non-Gaussian (Poisson or Johnson) noise N_k.

The matrix $\mathbf{F}$ is derived by approximating Fourier's heat equation (thermal conductivity reconstruction problem) using various approximation methods, e.g. multi-pole or Born approximations. As in almost all image reconstruction problems we have dealt with, these approximations generally yield ill-conditioned $\mathbf{F}$ and require regularization to stabilize the inverse. The regularization will be selected to constrain the 3D solution to a spatially smooth class of functions in accordance with a priori biometric information and also from surface information derived by observed cantilever displacements. We will also explore real time implementable algorithms which will involve methods such as: preconditioning, approximating the A matrix by circulant, block circulant, and other matrix structures, and other approximations of $\mathbf{F}$ for which fast algorithms can be used to solve for $\mathbf{X}_k$ (1).

1.4 Scan Optimization

Most imaging systems have a set of acquisition parameters that are under the experimenter's control and that can affect the final image quality. For example, in the thermal wave imaging the pattern of applied thermal stimulus is programmable. Rather than choosing these parameters arbitrarily, we propose to use statistical methods for optimizing estimation performance (based on extensions of the Cramer-Rao lower bound) [24] to optimize the acquisition parameters, extending our previous work on analyzing and optimizing imaging systems [25, 26].

1.5 Scan Registration

For multiple cantilevers, we may face a problem of registry. It may be difficult to ensure that the last line of one cantilever lies exactly one pixel spacing from the first line of the next cantilever. If the mechanics cannot ensure this, then we will investigate an image post-processing solution in which the system is designed to deliberately include a couple rows of overlap, and then we will apply well-known image registration algorithms (such as correlation based on an affine model) to combine the different sweeps. If processing speeds permit, we will also investigate the possibility of integrating this registration with the dynamical control model described above.

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