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Bayesian-Based
Enhanced - Magnetic Resonance Imaging
(Flow Systems)

FAQ and Responses

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1. Why is there a need to estimate flow parameters with a special method in Magnetic Resonance Imaging?

Magnetic Resonance Imaging has proven to be a revolutionary diagnostic radiological tool, due to its high spatial resolution and excellent discrimination of soft tissues. Magnetic Resonance Imaging provides rich information about anatomical structure, enabling quantitative anatomical studies of disease processes, the derivation of computerized anatomical atlases, as well as three-dimensional visualization of internal anatomy, for use in pre-operative and intra-operative visualization, and in the guidance of therapeutic intervention.

The role of dynamic imaging in medicine is of growing importance as a tool for diagnosis, treatment, and research. Most importantly is the role of flow studies inside the vascular tree: these range from flow studies in the heart, major arteries, and through replacement devices like valves, to more delicate studies of flow patterns in the brain.

For very large superficial vessels like the carotid, methods such as Doppler have proved very useful. Flow studies of smaller, deeper vessels have necessitated more complicated and invasive techniques such as the scanning of exogenously introduced radio labeled substances. Valuable as these techniques have been, the results have lacked resolution to provide detailed flow parameters on a small scale

Therefore, *there is a need to be able to provide higher resolution and detailed flow parameters for smaller/deeper vessels.* Bayesian methods for flow parameter estimates provide higher resolution and detail. The present invention resolves problems of resolution and deep tissue location, thus enabling the use of a non-invasive technique for virtually all flow studies on any scale available to MRI.

2. What are the clinical implications?

The immediate clinical implications are widespread. In the assessment of adequate blood flow, such as the determination of cardiac output, flow to the extremities or the head, the present invention provides a degree of accuracy and penetration to non-superficial vessels unavailable until now. This is especially useful in the evaluation of the extent of thrombotic/embolic strokes and myocardial infarctions, both past and in evolution by use of a non-invasive, zero radiation dose, real time procedure.

In addition to answering the “What is the flow in this vessel?” question, the present invention, Bayesian-Based MRI Enhancement for flow parameter, estimates magnetic resonance imaging, enables the examination of microscopic flow characteristics on an extremely small scale. This allows the examination of flow parameter gradients across a vessel diameter and the quantitative determination of turbulence regimes across hydrodynamic impedances such as heart valves, plaques, spasms, and malformations such as anneyurisms. This latter capability is very important in the design of intravascular prostheses such as valves, vessel replacements, stents, etc.

3. What are the basic physical principles behind Magnetic Resonance Imaging?

Nuclear Magnetic Resonance (NMR), also known as Magnetic Resonance Imaging (MRI), is fundamentally a process by which the magnetic moments of various nuclei are obtained. The nuclei are first immersed in a fairly strong but homogenous magnetic field. This field causes the nuclear magnetic moment of a nucleus to precess about an axis parallel to the direction of the field. The frequency with which the magnetic moment precesses is called the Larmor frequency. Then, a weak oscillating field is applied in a direction orthogonal to the homogenous field. When the frequency of the field oscillations is the Larmor frequency, a resonance condition is met and the nuclei are caused to jump from one quantum state to another.

All magnetic resonance experiments involve the transition of the nuclear spins from a given state to one of higher energy. In order to be detectable, two conditions must be satisfied [Robert Leighton, Principles of Modern Physics, (McGraw-Hill, New York, N. Y., 1959) p. 468-470.]. First, more nuclei must be in the lower states than in the upper ones, so that the upward absorptive transitions outnumber the downward induced emissive transitions, which return energy to the oscillator. Second, the nuclei in the upper state must have a means of returning to a lower state other than by emitting radiation. The first condition is satisfied when the populations of the various energy states are in statistical equilibrium at sufficiently low temperatures in a sufficiently strong magnetic field. The second condition is satisfied if there is a sufficiently strong coupling between the nuclear moment and the solid or liquid system in which it is situated. This coupling leads to nonradiative transitions of the nuclei, the energy being transferred to the crystal lattice where it appears as heat. This energy transfer called spin-lattice relaxation permits nuclear spins to return toward statistical equilibrium. Another relaxation mechanism is called spin-spin relaxation. It is due to the interaction between the magnetic moments of two nuclei. The effect of the spin-spin interaction is to cause the transverse component—orthogonal to the homogeneous magnetic induction field—of the magnetization to relax back to zero.

The phenomenon of nuclear magnetic resonance has been put to use as a powerful tool for discovering new properties of matter. This has been especially true in nuclear physics, chemistry, and most recently in medicine where NMR is called MRI. Numerical values of the magnetic moments provide information about the structure of the nuclei. "In chemistry much has been learned from the structure, or shape, of the resonances. Because of the magnetic fields produced by nearby nuclei, the exact position of a nuclear resonance is shifted, depending on the environment in which any particular nucleus finds itself. Measuring these shifts helps determine which atoms are near which other ones and helps to elucidate the details of the structure of molecules" [Richard P. Feynman, Robert Leighton and Matthew Sands, The Feynman Lectures on Physics, Vol. II, (Addison-Wesley, New York, N. Y., 1964) sec. 35, p. 10-12].

4. What is the Bayesian Method and how does it differ from classical statistical methods presently being used?

The Bayesian Method is based on Bayes' Theorem, which uniquely employs conditional probabilities. The following simple outline is a mini tutorial of the Bayesian Method. It highlights the structure and essential elements of the method:

- Bayes' Theorem — Simple Version:

$$P(\text{Hypothesis, Data} \mid I) \propto P(\text{Data} \mid \text{Hypothesis}, I) \times P(\text{ Hypothesis} \mid I),$$

where the symbol $\propto$ means proportional and the symbol

P(X | I) — Probability of finding (X | conditioned on all prior Information, | I).

- P(Hypothesis | I) Theorem — "Prior Probability"
  State of knowledge about the truth of the Hypothesis before analyzing current data. (knowledge of experimental results of various measurements.)

- P(Data | Hypothesis, I) — "Likelihood Function"
  Probability that the measured data is observed if the Hypothesis is true. Different models may be employed. These can be:

  * Empirical
  * Theoretical
  * Stochastic
  * Combination of Any/All

- P(Hypothesis | I) — "Posterior Probability"
  State of the knowledge about the truth of the Hypothesis in view of the measured data.

- Power of Bayes' Theorem — Relates the quantity of interest, the Probability that the Hypothesis is true given the data, to the Probability that we would have observed the measured data if the Hypothesis is true,

  P(Data | Hypothesis, I).

  This is the term we have the best chance of assigning a probability.

- Bayes' Theorem Encapsulates the Process of Learning — it builds upon all prior knowledge in addition to the present experimental results.

  * New Information can easily be incorporated to enhance the confidence of the Posterior Probability.

- Bayesian Probabilities vs Classical Stochastic Probabilities

  * Bayesian Probabilities: Conditioned probabilities that present a *degree-of-belief* or plausibility—how much something is thought to be true, based on the evidence at hand.

  * Classical Stochastic Probabilities: *Long-run relative frequency* with which an event occurred, given many (strictly an infinite number) repeated (experimental) trails. Seen as a tool to deal with "randomness."

Several more points should be made in the understanding of the power of the Bayesian Method:

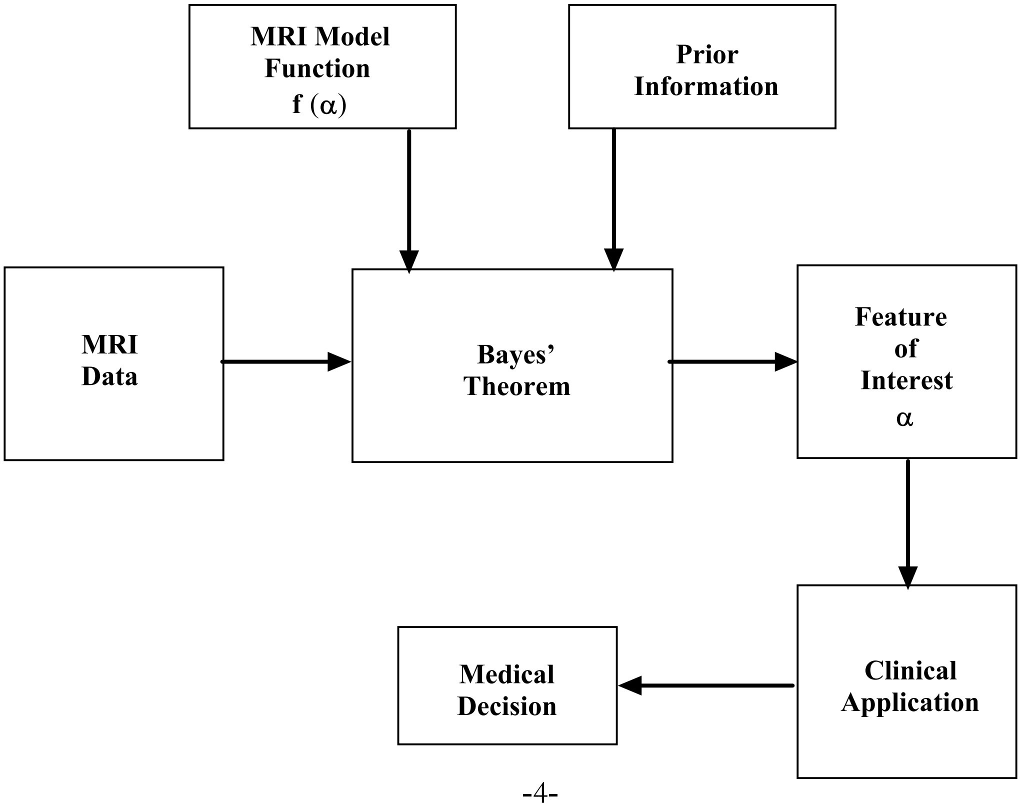
- The probability density is a function of all relevant parameters that enter into the modeling of the data.
- All parameters not of interest for the particular problem or issue being addressed are averaged over and effectively removed from the formulation. The result is a reduced probability density, which is a function only of the parameter(s) of interest. This is

formally termed nuisance parameter averaging. It leads to huge increase in accuracy of the parameter(s) under study.

- It is the only method that can incorporate prior information and also provide a measure of updated probabilities based on new evidence.
- It can provide validity of multiple hypotheses to model given data. This can give a quantitative measure of the goodness of fit of a given model.
- By contrast, current analysis involves traditional signal processing methods along with linear and / or non-linear least-squares estimation methods. That is, all the parameters that enter into the data modeling and simulations are either estimated or predetermined and fixed. The parameters of interest are thus weighted by the presence of the nuisance parameters eliminated in the Bayesian Method. Thus the correlations among the parameters bias the estimation of all the parameters. This ultimately limits the accuracy and signal to noise ratio of the method.

In summary, the Bayesian Method optimizes and determines the values of the all input parameters as well as the parameter(s) of interest as part of the calculation. The input values are used only as an initial guess to start the algorithm. The flexibility of being able to adjust the parameters in accord with the actual experimental data is a decided advantage over the use of predetermined, fixed parameters employed by current methods in use such as with the matched filter method. Moreover, the values of the parameters may be improved upon by the addition of a new knowledge of the physical situation in the form of empirical and/or theoretical models that may include features such as boundary conditions or perturbations. The Bayesian Method is a dynamic and unique method for parameter estimation, and prior to this disclosure has not been applied to MRI flow measurements. A summary flow chart of the methodology just described is shown below.

High Level Flow Chart of the System Methodology



5. Has the Bayesian Method been previously applied to Magnetic Resonance Imaging?

Yes, but neither in living tissue nor in flow studies. Brethorst [G. L. Brethorst Bayesian, *Analysis III—Applications to NMR Signal Detection, Model Selection and Parameter Estimation*, Journal of Magnetic Resonance, **88**, 571, 1990; Bayesian Spectrum Analysis and Parameter Estimation, Vol 48, (Springer-Verlag, New York, N. Y., 1988)] developed a Bayesian method for inverting nuclear magnetic resonance measurements–free magnetic induction decay measurements taken on a mixture of 63% liquid Hydrogen-Deuterium (HD) and Deuterium (D2) at 20.2 K–to obtain critical characterization parameters of a target molecular specie. His approach used a Gaussian-like Likelihood Function, which employed a simple single harmonic frequency Model Function and the assumption of background white noise. He then modified the Likelihood Function to include multiple harmonic frequencies, assumed not to have any interfering effects within the sample, which resulted in a somewhat standard Posterior Probability Function known as the Student-t Distribution. The Bretthorst method accurately estimated quantities such as spin precession frequencies, spin decay/relaxation rates, and spin magnetization. His results were markedly better than those obtained by stochastic methods. Additionally, the Bretthorst method has the ability to resolve very closely spaced frequencies if there is information (evidence) in the data. This fine structure is of particular importance in flow studies.

The use of the Bayesian method has enhanced the information provided by NMR free magnetic induction decay measurements on stationary systems. However, it has not been modified and applied to dynamic systems or in vivo measurements on patients where motion–intentional as well as unintentional–and other than white background noise are critical.

6. How is flow accounted for in a measurement technique—MRI—that has been traditionally applied to static systems?

The present invention, Bayesian-Based MRI Enhancement, applies Bayesian techniques to the analysis of complex MRI flow data to obtain parameters of interest such as velocity, acceleration, turbulence, and phase shifts due to flow gradients. This is done, in part, by uniquely integrating dynamic Model Functions into the Bayesian scheme. (Dynamic Model Functions mean parameterized Model Functions that are *time - dependent* in order to specifically address the flow nature of the problem.) MRI flow data, in particular, in vivo flow data, is infinitely more difficult to resolve than in vivo stationary data. The present invention, Bayesian-Based MRI Enhancement, uses a unique creative application of Bayesian probability methods to in vivo flow data is of extreme benefit in resolving this vastly more complex information. The basic equations for magnetization, known as the Bloch equations [W. S. Hinshaw and A. H. Lent, *An Introduction to NMR Imaging: From the Bloch Equation to the Imaging Equation*, Proc. of IEEE, **71**, 337 (1983)] have been rewritten to account for the motion of a fluid on which the MRI measurements are to be made.

Typically, the imaging is done in a process called *echo-planar* imaging in which data is simultaneously taken in multiple slices of the target system. A convenient technique for analyzing the data is to work in reciprocal or Fourier space. Once the transformation is made the incorporation of flow is made by multiplying the function by exponential functions decaying in Fourier space at a rate proportional to the spin-spin relaxation rate. To complete the picture of flow a kinematic equation describing the motion of a position vector within each slice was derived. This is then related to the "phase" function given as part of the general definition of the Fourier transform of the transverse magnetization of a slice. The differential of the time integrated phase functions, with and with flow included, contains all the necessary flow parameter information.

The full mathematical details are given in Xoetronics' pending U.S. Patent, Application Serial No. 09/781,035.

7. Is it possible to interface the new enhancement technology with existing MRI processing software products?

Yes, this is possible in two ways. The first way is to compile it with existing software packages so that it may run as a stand-alone if desired. The other way is to add on an interface module to existing packages so that it to may run as a stand-alone. The output images (either raw or processed) are fed into the software module for enhanced processing.

8. Can the new technology run in real time with existing computational resources?

Yes. The processing software will run on a number of platforms such as SUN workstations and personal computers. The software will be ported onto special purpose DSP chips embedded onto a hardware in the loop processing boards, which can be interfaced with windows based or unix based workstations. Since raw data will be used compression issues do not arise. Interfacing with other software must be done on a case-by-case basis with input from the software designers. However, this is a fairly straight forward procedure and no problems a foreseen.

9. Can the processing for estimating flow parameters be automated?

Succinctly put—Yes!

10. How long will it take to develop prototype software for demonstration?

It is possible to develop a prototype software package for demonstration with a six-month period. The development effort will require two software engineers with signal processing backgrounds and a radiologist. The computational resources (hardware) to carry out the project are available.

11. What is the lead-time after software prototype for clinical trials before the product is approved for commercial use?

Since the proposed software can be developed as add on software to existing packages the lead-time will be relatively short. It is expected to be approximately a year or less.

12. How can the Intellectual Property rights for the computer implemented Bayesian-Based Magnetic Resonance Imaging Enhancement (Flow Systems) and underlying algorithms be protected?

Traditionally, computer software, a process based on a mathematical formula, and a method of doing business were three types of intellectual property that were excluded from patentability. The U.S. courts have referred to these exceptions as the "mathematical algorithm" exception and the "business method" exception. The U.S. Supreme Court has upheld Federal Court decisions essentially indicating that computer software, a process based on a mathematical formula, and a business method are patentable subject matter. On January 11, 1999, the U.S. Supreme Court left intact the decision of the Federal Circuit Court in *State Street Bank*, which held that a computer system designed to implement an investment structure is patentable. This decision has opened the door to new and powerful ways to protect these kinds of intellectual property. This trend leads to the interesting situation in which software can be protected simultaneously by patent, copyright, and trade secret laws. A patent can protect a software idea, while copyright and trade secret laws can protect the details of the software as an unpublished work. This multifaceted legal protection can provide significant financial and competitive advantages for the software developer, as well as establish barriers. Essentially, computer software that utilizes a mathematical formula and methods for doing business are now patentable subject matter, which means that we have new and powerful ways to protect these kinds of intellectual property. Outside of the U.S. computer software that utilizes a mathematical formula is increasingly being recognized as patentable subject matter.

13. Please provide an Intellectual Property summary covering the Bayesian-Based Magnetic Resonance Imaging Enhancement (Flow Systems).

Pending patents include:

- US Application Serial No. 09/781,035 filed February 9, 2001, entitled Bayesian Methods For Flow Parameter Estimates In Magnetic Resonance Imaging, which claims priority from US Provisional Application Serial No. 60/181,823 filed on February 11, 2000.

Appendix

Overview of a Magnetic Resonance Imaging System

A conventional Magnetic Resonance Imaging system[1] is depicted in Fig. 1 below. The MRI machine is placed in an RF shielded room where data on the patient will be taken. This is to avoid spurious signals from the surroundings: both from external electronics as well as from signals generated by the driving electronics of the system itself. The probe part of the MRI machine houses magnetic cryostats for keeping the magnetic coils cool and in a peak operating range. There are essentially three sets of coils: gradient, receive and transmit coils. The patient is positioned on a patient table, which brings the patient into the magnetic field in such a way that the anatomy to be imaged is in the region where the field is homogeneous; this region is called the isocenter.

A host computer, located outside the RF shielded room, operates the MRI machine. A user requesting specific imaging information via acquisition commands mans the computer. The processed data is sent to the viewing section on the console. Here the user can display the images on the monitor and/or can reproduce them on a hard copy camera.

To do a targeted scan relevant patient statistics are first entered into the administration section on the console. The system is then instructed to do the required scan, including the geometrical parameters, the imaging method, and the sequence timing. (For new or experimental imaging the gradient field strength as a function of time for each direction x, y and z and the RF waveform must first be programmed into the memory of the host computer. This can also be done on the computer console.) The information is then forwarded to an operational area of the machine known in general as the "spectrometer." The spectrometer consists of the front-end-controller (controlling the magnet, gradients, RF transmitter and receiver, RF coil switches, etc.) and the data acquisition around the receiver (the receiver switches and the ADC (analog-to-digital converter).

Before the actual scan begins the spectrometer must perform an initialization sequence: tune the synthesizer frequency, ω_o, to the gyromagnetic frequency; tune the RF receiving coils; and, the RF power and receiver gain must be adjusted to the specs of the designated measurement, etc.

Now the Spin Echo sequence can start. All components, except for the magnet, turned off a selection of the field gradient is. When the field gradient reaches it preset required value the RF power amplifier is engaged and its output is switched with frequency ω_o. This signal (also known as the excitation pulse signal) is modulated in the waveform generator and fed into the power amplifier. The RF signal, which can be AM or FM modulated, drives a current in the transmit coil to produce the required magnetic induction, B_{RF}, within the center of the coil. Simultaneously, the receiver coils are detuned and the pre-amplifier blocked so that the large transmit signal will not burn out the pre-amplifier. When the RF pulse is of sufficient magnitude, the output line of the power amplifier is switched to the matched load again. The output noise of the power amplifier with zero input signal is high enough that it could mask the MR signal to be measured and so the switching is a necessary function. The selection gradient is now switched off. Because of the high coil inductance and the

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[1] See, M. T. Vlaardingerbroek and J. A. den Boer, Magnetic Resonance Imagining, (Springer-Verlag, New York, N. Y., 1996)

gradient-amplifier voltage the reduction of the gradient field is not instantaneous but occurs in some small time interval. As a result of this procedure, spins in a thin slice of the target are aligned.

Next, the dephasing gradient and the phase-encode gradient are switched on and brought to the required strength, which has been programmed into the operational specs of the spectrometer. When the gradient pulses have the required surface value, i.e., the integral of the gradient over time, they are switched off and the refocusing pulse can now be applied. This 180° RF pulse is usually slice selective and can be applied to the same slice as the excitation RF pulse. Its waveform is similar to that of the excitation pulse but with twice the amplitude or four times the power. In single-slice methods, slice selectivity of the refocusing pulse may be left out, making the pulse of shorter duration possible.

When the refocusing RF pulse cycle is finished the read-out gradient is switched on. During this gradient pulse the receiver coil is in a tuned state and the receiver is activated. Concurrently, the magnetization is measured and the ADC samples the received signal in predetermined sampling time interval. The system is then allowed a period of time to relax to its initial configuration so that the spectrometer can proceed to image the next elemental slice in the scan sequence. The process is repeated until the whole scan is completed. Slice sample data are sent to the array processor where fast Fourier transforms are performed on the data. When the slices are transformed and reassembled, an image results. This image is sent to the view section on the console.

Usually after this first scan more scans of the same anatomical area follow. These scans are taken of slices positioned on the basis of the first image. The user can select the orientation and the off-center distance of the slices addressed in such scans.

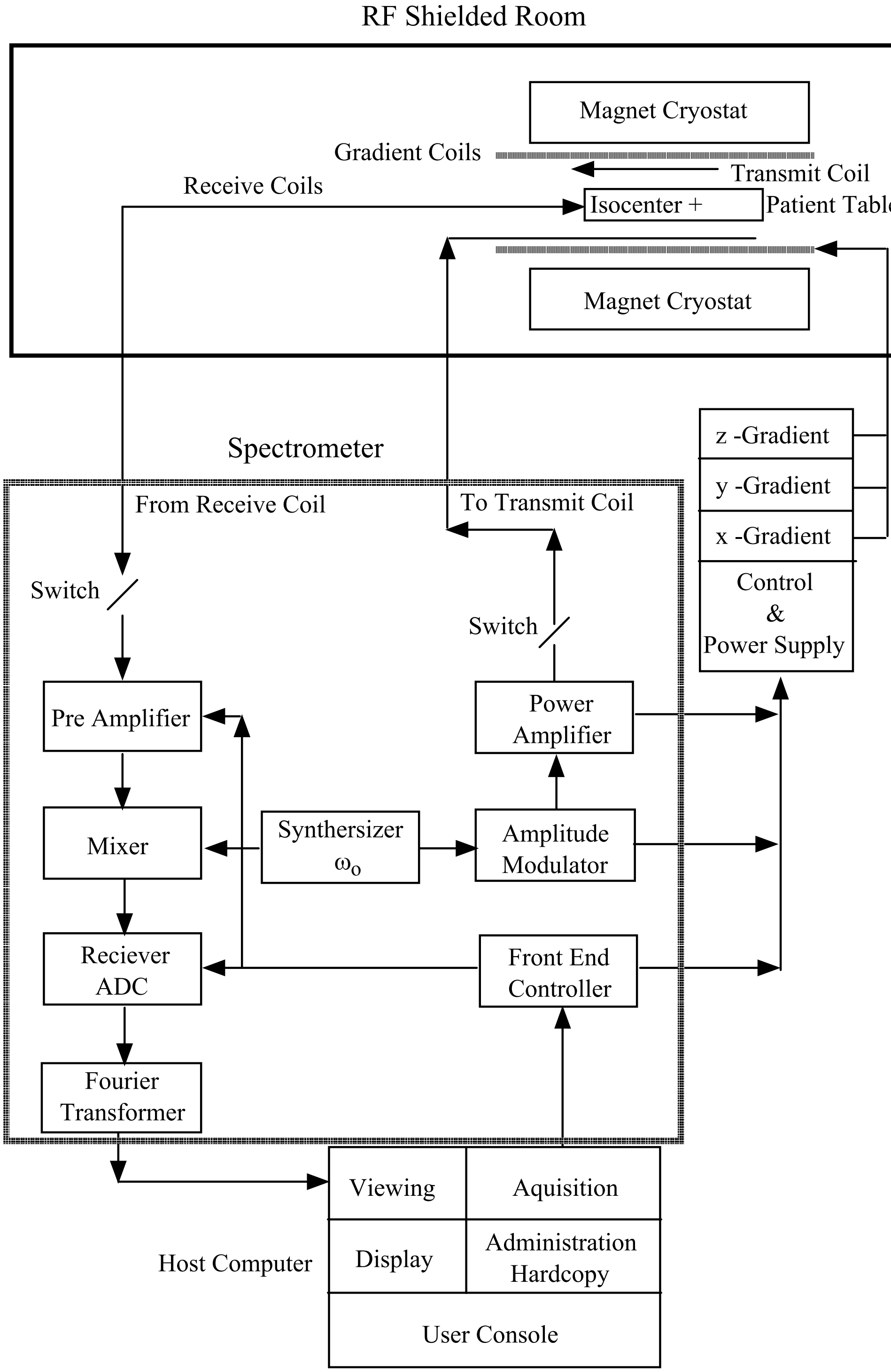

Fig. 1 Typical Magnetic Resonance Imaging System